INSULIN RESISTANCE IN PSORIASIS PATIENTS VERSUS NORMAL PERSONS IN A TERTIARY CARE HOSPITAL - A COMPARATIVE STUDY

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CERTIFICATE

This is to certify that the dissertation entitled "**INSULIN RESISTANCE IN PSORIASIS PATIENTS VERSUS NORMAL PERSONS IN A TERTIARY CARE HOSPITAL - A COMPARATIVE STUDY**" is a bonafide work done by **Dr. V. S. Uma Maheshwari** in partial fulfilment of the university rules and regulations for award of **M.D Biochemistry [Branch-XIII]** under my guidance and supervision during the academic year 2015-2018.

9/10/17

Dr. R. Nagendran, M.D.,
[Guide]
Professor and HOD
Department of Biochemistry
Sree Mookambika Institute of
Medical Sciences [SMIMS]
Kulasekharam [K.K District]
Tamil Nadu -629161

9/10/2017

Dr. S. Jaya, M.D.,
[Co- Guide]
Professor
Department of Biochemistry
Sree Mookambika Institute of
Medical Sciences [SMIMS]
Kulasekharam [K.K District]
Tamil Nadu -629161

Dept. of Bio-Chemistry
MEDICAL SCIENCES, KULA-KHARAM

Rema. V. Nair

Dr.Rema. V. Nair, M.D., D.G.O.,
Director
Sree Mookambika Institute of
Medical Sciences [SMIMS]
Kulasekharam [K.K District]
Tamil Nadu -629161

DR. REMA V. NAIR M.D.,D.G.O.
DIRECTOR
Sree Mookambika Institute
Of Medical Sciences
Kulasekharam

SREE MOOKAMBIKA INSTITUTE OF MEDICAL SCIENCES
KULASEKHARAM-629

DECLARATION

I Dr. V. S. Uma Maheshwari hereby submit the dissertation titled **"INSULIN RESISTANCE IN PSORIASIS PATIENTS VERSUS NORMAL PERSONS IN A TERTIARY CARE HOSPITAL - A COMPARATIVE STUDY"** done in partial fulfilment for the award of the degree **M.D Biochemistry [Branch-XIII]** in Sree Mookambika Institute of Medical Sciences, Kulasekharam. This original work is done by me under the guidance and supervision of Dr. R. Nagendran, M.D.

9/10/17

Dr. R. Nagendran, M.D.,
(Guide)
Professor and HOD
Department of Biochemistry
Sree Mookambika Institute of
Medical Sciences (SMIMS)
Kulasekharam.

Dr.V. S. Uma Maheshwari,
Postgraduate
Department of Biochemistry
Sree Mookambika Institute of
Medical Sciences (SMIMS)
Kulasekharam

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ABBREVIATIONS

HLA - Human leukocyte antigen

TNF α - Tumour Necrosis Factor alpha

Th 17 - T helper cell 17

IL - Interleukin

IR - Insulin Resistance

VEGF - Vascular endothelial growth factor

CD8 - Cluster of differentiation 8

T-reg - Regulatory T-cell

APCs - Activated antigen-presenting cells

Jak 2 - Janus kinase 2

Tyk - Tyrosine kinase

STAT 3 - Signal transducers and activation of transcription 3

PASI -Psoriasis Area and Severity Index

AAD - American Academy of Dermatology

2D NMR - Two-dimensional nuclear magnetic resonance spectroscopy

SNARE -Soluble N-ethylmaleimide-sensitive factor activating protein receptor

IR-A, IR-B - Insulin receptors

MAPK - Mitogen-Activated Protein Kinase

ras - Rat sarcoma

mTOR - Mammalian Target of Rapamycin

FoxO1 - ForkheadBoxO1.

G-6-Pase - Glucose-6-phosphatase

LXR - Liver X Receptor

NEFA - Non-esterified fatty acid

PPAR-α - Peroxisome Proliferator Activated Receptor alpha

ET-1 - Endothelin-1

HOMA-IR - Homeostasis Model Assessment for Insulin Resistance

QUICKI - Quantitative Insulin Sensitivity Check Index

MS - Metabolic Syndrome

ATP III - Adult Treatment Panel III

IRS - Insulin receptor substrate

IGT - Impaired Glucose Tolerance

IDF - International Diabetes Federation

PAI -1 - Plasminogen Activator Inhibitor-1

IFN-γ - Interferon – gamma

RAR - Retinoid acid receptors

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INTRODUCTION:

Psoriasis is a multisystem disease of unknown origin and is universal in occurrence. The most characteristic lesions consist of scaly, erythematous and sharply demarcated plaques present particularly over the extensor surfaces.[1] Its prevalence in different population varies from 0% to 11.8%. In India it varies from 0.44 to 2.8%. It is twice more common in men when compared to women. Psoriasis may begin at any age but more common to appear between 15 and 30 years.[2]Depending upon HLA association, Henseler and Christophers had proposed two forms of psoriasis- type I with age of onset before 40 years and HLA associated, and type II with age of onset after 40years and lacking HLA association.[3]

Psoriasis has a genetic basis and is characterized by complex alterations in epidermal growth and differentiation together with multiple biochemical, vascular and immunological changes and also has some relation with nervous system. Based upon population studies, the estimated risk of psoriasis in an offspring is 41% if both parents are affected, 14% if single parent is affected and 2% if parent or sibling is not affected.[4]

Psoriasis is a chronic T – cell mediated inflammatory skin disease with a prevalence of 2%. The improvement of symptoms on treatment with ciclosporin was the first indication that it is T – cell mediated. Studies have also demonstrated that the infiltrates in psoriatic plaques are composed of Th1 cells and they are producing Th1 cytokines (example – TNF α). The improvement of psoriasis with

anti – THF therapies supported that psoriasis is a T cell type 1 or Th – 1 mediated disease. More recently Th 17 lymphocytes expressing IL-17 and Th 17 cytokines were found in psoriatic lesions, indicating that these cells are also involved in pathogenesis of psoriasis.[5]

Changes in skin may signal more serious health issues and they frequently serve as a marker for internal diseases. Insulin plays a central role in metabolic system and has an important role in maintaining homeostasis and physiology of the skin. In healthy persons, insulin regulates the balance between differentiation and proliferation of keratinocytes and form the equilibrium needed for the formation of epidermal structure. Insulin Resistance (IR) is defined as the inability of a known quantity of insulin to increase the glucose uptake and utilization of cells in an individual as it does in a normal population. In chronic inflammatory conditions like psoriasis, high levels of proinflammatory cytokines induce IR leading to an increased proliferation of basal keratinocytes and, at the same time deny access to differentiation.[6]

The chronic inflammatory nature in psoriasis is thought to predispose the patients to other diseases with inflammatory component, of which the most notable are cardiovascular and metabolic disorders. This concept is supported with studies that show psoriasis in association with cardiovascular risk factors like diabetes, obesity, hypertension and dyslipidemia. The patients with severe psoriasis have high rate of obesity and diabetes than patients with mild psoriasis.[7]

The mechanisms for this association is uncertain, but proinflammatory cytokines like tumour necrosis-α have been demonstrated to decrease the activity of insulin, thus contributing to IR. Therefore inflammation is not only found in association with obesity but also with IR even when there is no increase in total body fat.[8]

Associations between psoriasis and metabolic diseases have been increasingly recognized. Various epidemiological studies are establishing these association and they are determining the directionality of these associations and bringing the role of psoriasis as an independent risk factor for all these outcomes.[9]

However there are many unanswered questions concerning the link between psoriasis and metabolic derangements. There is a scarcity of studies on the natural spectrum of psoriasis and screening procedures for MS in psoriasis patients.[10] On the basis of the present knowledge, new guidelines are issued aiming to actively identify metabolic disease and other cardiovascular risk factors in psoriasis patients so that these factors are properly addressed.[11]

AIMS AND OBJECTIVES:

1. To estimate the level of insulin resistance in psoriasis patients.
2. To study the other associated biochemical parameters like fasting plasma glucose, serum high density lipoproteins and serum triglycerides in psoriasis patients.

REVIEW OF LITERATURE:

General facts on psoriasis:

Today, psoriasis is one of the most common inflammatory skin diseases disturbing the Caucasian population worldwide. Psoriasis is a persistent, immune-mediated, inflammatory and proliferative skin disease with 2 to 4% occurrences of new cases in the general population.

Psoriasis vulgaris is the most common form. The clinical features of psoriasis vulgaris patients are erythematous-squamous lesions seen mainly on the extensor areas of elbows, knees and scalp. The lesions may remain stable for a long duration or become more intense spreading to the whole body surface area. Psoriasis can be categorized in terms of body surface area as mild, moderate and severe forms when 2%, 2-10% and over 10% respectively of body surface area were affected.

Psoriasis can be classified into type I characterized by an onset before 40 years with a positive family history and associated with HLA- Cw6, HLA- DR7; late onset type II with an onset after 40 years of age, having a negative family history and not associated with HLA. Psoriasis shows a multifactorial and polygenic pattern associated with genetic variations. There are several factors that contribute to exacerbation of disease such as stress, smoking, infections and medications like beta blockers, anti-inflammatory drugs. But the etiopathogenesis of psoriasis is not yet completely elucidated.[12]

Prevalence of psoriasis:

The general prevalence of psoriasis in India was ranging from 0.44 to 2.8%and the point prevalence of psoriasis is 8% .The male: female ratio was 1.1:1. Highest prevalence was found in 21-30 and 41 -50 age groups each forming 25%. Chronic plaque psoriasis is the most common clinical type (50%). The commonly involved sites were the palms and soles followed by scalp. Bedi had reported a family history of psoriasis in 14% of his patients.[13]

A hospital based cross sectional study done at the department of Dermatology, have found 2.4% incidence of psoriasis on the basis of characteristic clinical features such as presence of scaly patches with silvery scales. This study included various types of psoriasis like palmoplantar, scalp, pustular, flexural, nail and erythrodermic psoriasis. This incidence corresponds with 2.3% incidence of a North Indian study at a tertiary health care hospital. Okhandiar et al., had found an incidence of 0.44 to 2.2% among total skin patients in his comprehensive study. [14]

Etiopathogenesis of psoriasis:

Psoriasis is a T lymphocyte based disease identified by the characteristic appearance of raised, red scaly skin lesions. The major pathological changes in these lesions are epidermal hyperproliferation together with abnormal differentiation, angiogenesis, vascular proliferation and inflammatory infiltration in the dermis. This epidermal hyperplasia and inflammation are responsible for the pathogenesis of psoriasis. The inflammatory infiltrate is believed to be due to the production of large amount of cytokines by keratinocytes. The increase in

keratinocyte proliferation is due to T-cells as evidenced by in vitro studies. The cytokines cause T-cell activation which again secretes cytokines and growth factors leading to further proliferation of keratinocytes establishing a vicious cycle. Thus T cells are found to play a direct role in pathogenesis of psoriasis. Mor et al., in his experiments had proved T-cells synthesize and secrete VEGF. Immunostaining had confirmed that VEGF is a mediator in angiogenesis and epidermal hyperplasia.[15]

The involvement of T-cells in psoriasis was discovered by its improvement with T-cell suppressive agents. T-cells are of two subtypes: CD8+ cytotoxic T-cells and CD4+ helper T-cells. Both these subtypes are found to be increased in psoriatic skin lesions. Initially only Th-1 and Th-2 cells are identified and was thought to be responsible for allergies and autoimmune responses. However, in recent years, a complex array of phenotypes of CD4+ helper cells are described including T-reg (regulatory T-cell), Th 17, Th 22, and Th 9 cells. Psoriasis is now considered to be mainly mediated by IL-17 producing Th 17 cells. This concept is confirmed by success in treatment with either IL-17 targeting drugs like Secukinumab, Bimekizumab, and Ixelkizumab or IL-17 receptor blockers like Broadalumab.[16]

Histopathology of psoriasis lesion:

The phagocytic system of skin consists of heterogenous cells that belong to two cell lines. They are monocyte-macrophage and dendritic cell lines. These cells are specialized phagocytes playing significant roles in cleansing of apoptotic cells, harmful molecules and also in defense against infections. The dendritic cell lines include Langerhans cells and dermal dendrocytes. In psoriatic lesions, increase in

dermal dendritic cells and decrease in epidermal dendritic cells especially Langerhans cells are observed. In psoriasis these dendritic cells and Langerhans cells modify T cell proliferation and release of cytokines. Langerhans cells have an anti-inflammatory role, hence decrease in their levels in psoriasis prolongs the inflammatory reaction.[17]

Autoimmune changes in psoriasis:

The autoimmune changes in psoriasis are characterized by dermal hyperplasia and infiltration of skin by immune cells that have migrated from blood. The histological features seen in psoriatic skin are keratinocyte hyper-proliferation, dermal angiogenesis and infiltration of inflammatory cells like T lymphocytes, neutrophils, monocytes and macrophages. Th-1 and Th-17 cytokines are found in psoriatic skin, together with other interleukins like IL-17A, IL-17F, IL-19, IL-20, IL-22, IL-23, IL-24, IL-26 and TNF-α in serum and skin lesion. Th-17 cells are a subset of CD4+ T cells. Th-17 cells in addition to IL-17 also secrete IL-21, IL-22, IL-23. IL-17 secreted by these cells play a regulatory role in chronic inflammation linking beneficial and pathological effects of immune system paving way for autoimmunity.[18]

Th1/Interferon pathway was originally implicated in this immune dysregulation. Now it was found out that Th-17/IL-23 pathway plays a significant role. IL-23 is the key cytokine that facilitates differentiation of T cells to Th-17 cells. IL-23 stained cells are seen in psoriatic skin lesions. It is produced by keratinocytes and also by activated antigen-presenting cells (APCs) like Langerhans

cells, macrophages and dendritic cells. The IL-23 binds with the IL-23 receptor present on T cells and form a complex.

This complex activates the Jak 2 and Tyk, the members of Janus family of kinases leading to phosphorylation of signal transducers and activation of transcription 3 (STAT 3). This triggers the differentiation to Th-17 cells. Th-17 cells secrete mainly two cytokines, IL-17A and IL-17F in addition to IL-21, IL-22, IL-26 and interferon gamma. All these cytokines activate the cascade of inflammation and provoke irregular replication and maturation of cells in psoriasis. Thus Th17/IL-23 pathway leads to chronic inflammation. IL-17 also stimulates angiogenesis and tissue modeling.[19]

Genetic basis of autoimmunity in psoriasis:

Genome-wide association studies evaluated gene expression in psoriasis and normal skin samples and identified genes relevant to the disease mechanism. A meta-analysis of microarray data had shown an enhancement of genes and expression at high levels in keratinocytes, T-cells and innate immune cells in association with elevated expression of genes in psoriasis lesions. From this it is understood that psoriasis is an auto-immune inflammatory disease that depends on interactions among multiple cell types from the skin such as T-cells, dendritic cells, macrophages, keratinocytes together with the adaptive and or innate immune systems. The cells release cytokines which reinforce the inflammatory cascade resulting in the appearance of plaque like lesions coated with silvery scales.

Development of inflammatory infiltrate is a characteristic feature of psoriasis lesions.[20]

Clinical types of psoriasis:

Psoriasis shows a wide spectrum of cutaneous manifestations with varying clinical features and severity. Various forms of this dermatosis can be present at the same time. All the lesions of psoriasis share the common characteristics which include erythema and thickening with round, oval or polycyclic borders. The size of the lesions varies from a pinhead till 20 cm diameter. The regions frequently involved are knees, elbows, scalp, lumbosacral region, and genital area.

Psoriasis is classified by its clinical appearance into 2 groups: pustular and non-pustular lesions. Non-pustular type includes psoriasis vulgaris, guttate psoriasis, erythrodermic psoriasis, palmoplantar psoriasis, inverse psoriasis, and psoriatic arthritis (PsA). Pustular psoriasis includes generalized pustular psoriasis (von Zumbusch type), localized pustular psoriasis and impetigo herpetiformis.

1) Psoriasis vulgaris: It is the most frequent clinical form constituting 90% of psoriasis cases. It present as sharp bordered erythematous plaques with pearlescent squamae covering over it. The lesions are symmetrically distributed over elbows, knees, scalp, and sacral region with a probable predilection of trauma. Scraping of the plaque exhibit layers of white lamellae followed by candle wax referred as wax spot phenomenon. Further scraping reveals a wet layer pathognomonic of psoriasis called last membrane phenomenon followed by erythematous background with

bleeding foci seen as small red pinpoints termed as Auspitz sign. Healed psoriatic plaques show a hypopigmented macular ring called Woronoff ring.

2) Guttate psoriasis: This type is frequently observed in children and young adults with sudden onset of small droplets like lesions generally following streptococcal infections. The lesions are seen on the scalp, face, trunk and proximal part of extremities.
3) Erythrodermic psoriasis: It is a generalized form with predominant erythematous lesions affecting nearly 80% of body surface area. There is widespread vasodilatation and hypothermia.
4) Palmoplantar psoriasis: There is symmetrical involvement of palms and soles with predominant squamae more frequently affecting the thenar regions. Erythema is not common, but if present will appear as a pinkish-yellow lesion.
5) Psoriatic arthritis (PsA): Arthritis can be manifested either before, during or more commonly after skin manifestations. It can be seen in different clinical forms. Moll and Wright described 5 subgroups in psoriatic arthritis.

a) Classical type: The lesions are seen in distal interphalangeal joints of hands and feet with frequent nail involvement.
b) Asymmetric oligoarticular arthritis: The most characteristic form of joint involvement is seen in this type. The knee joints, metacarpophalangeal, metatarsophalangeal, proximal and distal interphalangeal joints are asymmetrically affected.

c) Symmetric poliarticular form: Distal interphalangeal joints are frequently involved in this form and may be complicated by bony ankylosis.

d) Arthritis mutilans: This form presents with progressive osteolysis of phalangeal and metacarpal bones and also sacroiliitis.

e) Spondylitic form: Isolated spondylitis is rare and generally associated with peripheral arthritis. Though this form resembles ankylosing spondylitis, it has a better prognosis due to less severe joint ankylosis.

6) Inverse psoriasis: Lesions of this variety are localized in skin folds and present as bright red fissured plaques with distinct contours. This is also called flexural psoriasis and is common in obese individuals.

7) Generalized pustular psoriasis: It is a rare form frequently affecting young individuals. It has a sudden onset with high fever, lassitude, polyarthralgia and an erythematous background. The disease progresses with drying and eruption of new pustules.

8) Impetigo herpetiformis: This rare form is also called generalized pustular psoriasis of pregnancy is characterized by erythematous lesions which start at the flexural regions, get covered with pustules and then may agglomerate. The mucous membranes and skin are involved with itchy, foul smelling and burning sensation. There can also be deterioration of general health with fever, shivering, lassitude, nausea and vomiting. It is named after its occurrence in last trimester of pregnancy.

9) Localized pustular psoriasis:

It is of 2 forms: Barber's pustular psoriasis and acrodermatitis continua of Hallopeau .

a) Barber's pustular psoriasis: It is a chronic, recurrent form occuring frequently in women and accompanied with family history. Clinically 2 – 4 mm sized pustules are observed on palmoplantar region, and especially erythematous on thenar and hypothenar regions.
b) Acrodermatitis continua (Hallopeau disease): It is a proximally progressing skin disorder affecting fingers and toes with sterile pustular eruptions with sequelae of loss of nails and distal phalanges in severe cases. Pustules may get joined to form polycyclic, purulent, fluid-filled vesicles.

Clinical types of psoriasis are not a determinant of severity or progress of disease. It is important in treatment aspect.[21]

Severity of psoriasis:

Psoriasis is classified into mild, moderate and severe depending on erythema, induration and desquamation of plaques and the amount of involved body surface area. The classification based on body surface area is done using PASI (Psoriasis Area and Severity Index).[22]

Most trials of psoriasis patients are restricted to most common psoriasis vulgaris form. The commonly used measurement in psoriasis is Psoriasis Area and Severity Index (PASI) which gives a quantitative assessment of burden of psoriasis

lesions. It is based on how much is the body surface area involved and how much is the degrees of severity of erythema, induration, and desquamation or scaling.

The PASI was calculated based on following parameters:

1. Numbers 0 to 4 is given for the degree of severity of erythema, induration and scales.

2. The percentage of lesion in each area is graded as 0 to 6 as

0 = 0%, 1 = <10%, 2 = 10–29%, 3 = 30–49%, 4 = 50–69%, 5 = 70–89%, and 6 = 90–100%.

3. Number assigned for the weight of each region such as

0.1 for head and neck,

0.2 for upper extremities,

0.3 for body, and

0.4 for lower extremities.[23]

The formula can be made by abbreviating the prerequisites as follows

Head -h, trunk-t, upper extremity- u, lower extremity-l

Surface area involved – A

Erythema – E,

Infiltration – I, Desquamation – D

Formula for PASI is

$$0.1(Eh + Ih + Dh)Ah + 0.2(Eu + Iu + Du)Au + 0.3(Et + It + Dt)At + 0.4(El + Il + Dl)Al.$$

The calculated score ranges from 0-72.[24]

The severity of psoriasis is classified as moderate with PASI score between 10 and 20, severe when it was above 20.[25]

Fredriksson and Pettersson developed PASI in 1978 to evaluate the clinical efficiency of psoriasis treatment. American Academy of Dermatology (AAD) had recommended the PASI score and percentage of body surface area as the measures to assess extent of psoriasis while planning for treatment.[26]

Based on surface area of skin involvement, psoriasis is classified into three discrete categories: mild psoriasis affecting ≤ 2% of body surface area, moderate affecting 3 to 10% of body surface area and severe affecting > 10%.

A cross sectional study by The Health Improvement Network of UK found out that psoriasis is associated in a dose-response fashion with metabolic syndrome (mild cases show a 22% increase in Odds of metabolic syndrome, 56% in moderate and 98% in severe psoriasis).

According to National Psoriasis Foundation, psoriasis globally affects more than 125 million people. It is the most common type 1 T helper cell inflammatory disease. The proinflammatory state associated with psoriasis is the dragging force towards development of metabolic syndrome. In these patients, Th1 inflammatory

cytokines like TNF-α, IL-1 and IL-6 are increased in blood and skin. Inflammatory mediators affect insulin signaling, lipid metabolism and adipogenesis. Inflammation induced IR may lead to a systemic IR state. Increase in odd's of raised serum glucose and triglycerides are seen in psoriasis patients independent of obesity effect.[27]

Psoriasis and comorbidities:

The etiology of psoriasis remains to be identified. Evidences through scientific studies suggest that psoriasis is a complex disorder coordinated with the interplay between multiple genes. Psoriasis and its comorbidities together have a significant overlap in the variations of action in similar set of genes. The link between psoriasis and its comorbidities was coined as "diseasome".

Network medicine studies at Vellore Institute of Technology University have found out the molecular association between psoriasis and its comorbidities. The number of genes or proteins shared between psoriasis and T2DM were 312 of which 26 proteins are directly connected 210 proteins interact through partnering with other proteins. Similarly, the number of genes or proteins shared between psoriasis and MI (myocardial infarction) were 31 out of which 7 proteins are connected directly and 49 proteins are related indirectly.

This study had found that the psoriasis associated comorbidities are interrelated at the molecular level shared by common genes in addition with the level of proteins, biological processes and pathways. This study had provided an evidence for reality of a shared component hypothesis between psoriasis and its five

common comorbidities for instance MI, T2DM, obesity, rheumatoid arthritis and Alzheimer's disease. The study of these molecular connections not only aid in anticipation and management of psoriasis but also serves as a starting point for diagnosis and treatment of its comorbidities.[28]

The complex pathology of psoriasis requires elucidation of genetic, genomic, proteomic and metabolic elements for its molecular definition. Davidovici et al., hypothesized that inflammatory products could have been synthesized in the skin and released by diffusion through the cutaneous endothelium into the systemic circulation. The key mediators of inflammation in psoriasis are cytokines - tumor necrosis factor-α (TNF), interleukin – 17 (IL-17), or interferon – γ, (IFN-γ). IL-17 and TNF have additive and synergistic effects on modulating gene expression in keratinocytes.

Skin biopsy study by Mayte Suárez-Fariñas observed over expression of renin, cytotoxic T-lymphocyte antigen (CTLA)-4 and Toll-like receptor (TLR)-3 genes and their protein products at higher levels in psoriasis skin. Renin gene is involved in rennin-angiotensin pathway leading to aldosterone release and vasoconstriction. The CTLA-4 gene is identified in the functional pathway of metabolic diseases.

TLR3 signaling stimulates keratinocytes, releasing more proinflammatory cytokines, TNF and IL-8 and also activates IFN- and TNF-stimulated gene products. Thus there is increased expression of inflammatory cytokines or proteins responsive to these cytokines with a corresponding increase in mRNA in psoriasis

lesions. These gene products are linked to functional pathways leading to metabolic diseases suggesting a potential link between altered gene transcription in psoriasis skin and its comorbid diseases.

This link between psoriasis and metabolic comorbidities can be explained by two mechanisms. First is the hormone like proteins produced by psoriatic plaques for example renin and vascular endothelial growth factor. Second is the association of dysregulated gene expression present in psoriasis lesions with metabolic pathways leading to atherosclerosis, PPARα &RAR activation and leptin signaling.[29]

Metabolic derangements in psoriasis:

Psoriasis is characterized by local and also systemic escalation of proinflammatory cytokines. These proinflammatory cytokines in chronic inflammation are accused of augmenting the process of atherogenesis and peripheral insulin resistance leading to hypertension and T2DM respectively. Moreover recent studies showed that psoriasis is in association with other metabolic disorders such as dyslipidemia, abdominal obesity, insulin resistance, and even cardiac disorders. These findings suggest that psoriasis patients are preconditioned to DM, hypertension and metabolic syndrome. Of these DM is said to occur at any age and HT occur with higher rates as age advances.

The prevalence of metabolic syndrome is found to be high in psoriasis patients particularly after the age of 40 irrespective of the severity and duration of psoriasis. The study of Ilkin Zindancı in Turkey concluded that psoriasis

predisposes to DM, hypertension, and MS and the prevalence of MS is increased by 3-fold. Therefore they recommended evaluating psoriasis patients for MS.[30]

MS also called insulin resistance syndrome or Syndrome X is a combination of predictors of cardiovascular disease risk. It includes central obesity, hypertension, glucose intolerance and dyslipidemia. A study conducted at Department of Dermatology, Pusan National University Hospital have found out that there is no statistically significant difference in MS between psoriasis and control group after adjusting for age and gender but the triglycerides level is higher (42.7%) in psoriasis when compared to controls (26.2%) with a p value of <0.001. Careful attention should be paid in psoriasis patients to look for dyslipidemia concentrating more on triglyceride levels.[31]

Psoriasis and components of MS:

The MS if present can be diagnosed on the basis of presence of≥3 criteria of the modified National Cholesterol Education Program's Adult Treatment Panel III as follows:

waist circumference >102 cm in men or>88 cm in women,

hypertriglyceridemia ≥150 mg/dL,

high-density lipoprotein cholesterol <40 mg/dL in men or <50 mg/dL in women,

blood pressure ≥130/ 85 mmHg and

fasting plasma glucose ≥100 mg/dL.

Psoriasis is associated with significant morbidity affecting the quality of life even with limited body surface area involvement. Globally several studies have reported association between psoriasis and metabolic syndrome including obesity, diabetes, dyslipidemia, hypertension and recently atherosclerosis. But in India, there is a paucity of data on this association despite evidences suggest that Indians are genetically and environmentally more prone to develop metabolic syndrome. A cross-sectional study conducted at All India Institute of Medical Sciences, New Delhi had found a linear trend of increase in metabolic syndrome with increasing degree of severity of psoriasis in patients compared to controls. Dyslipidemia is the most common parameter whose values are inconsistent among various studies.[32]

The pattern of dyslipidemia found in metabolic syndrome characterized with elevated triglycerides and low HDL cholesterol is reported to be in association with psoriasis. Several studies like El Asmi et al. analysis of Tunisian psoriatic group and Damevska et al., study have shown hypertriglyceridemia in psoriasis patients. The relation between psoriasis and IR is also well documented. Several studies have underlined a link between impaired glucose metabolism and psoriasis. An observational study done by Brauchli et al., has revealed an increased risk of DM in psoriasis patients than in psoriasis-free group.[33]

Psoriasis and dyslipidemia:

A diagnosis of dyslipidemia can be made based on the following levels: triglycerides ≥150 mg/dl, or high-density lipoprotein cholesterol (HDL-C) ≤ 40 mg/dl in men or ≤ 50 mg/dl in women. A study at Federal University of Bahia had

shown that dyslipidemia was associated with psoriasis even after adjusting other known confounding factors. [34]

Genome wide association studies (GWAS) has found out that there is a significant genetic overlap between dyslipidemia and immune mediated disorders. There is sharing of susceptibility loci between them. The genetic loci that are shared with triglycerides is in loci 88, with LDL is in loci 87 and with HDL is in loci 52. These shared loci may be associated with overlapping of the pathophysiology between these two conditions. Atherosclerosis itself is a chronic inflammation of arterial walls together with sub-endothelial accumulation of lipids. There is experimental evidence which supports that inflammation plays a key role in atherosclerotic plaque formation.[35]

The proinflammatory cytokines elevated in psoriasis for example TNF IL-1 or IL-6 affect the metabolism of lipids leading to a high frequency of dyslipidemia. Studies at Brazil, Japan and Israel have shown 67%, 34.3% and 56.9% respectively of dyslipidemia in psoriasis patients. Research at the University clinical center Tuzla have taken composition of lipids in dyslipidemia associated with psoriasis as a subject of interest and found that not only overall cholesterol is increased, more significantly there was hypertriglyceridemia (39%) and a lowered value of HDL (36%). The average age of psoriatic affected by this dyslipidemia was 48.76years.[36]

Recent studies by Medical University of Graz, Austria have provided evidence that inflammation impairs the function of HDL and hence the reverse cholesterol transport. HDL is a complex lipoprotein which exerts athero-protective

activity by promoting cholesterol efflux from the macrophages through reverse cholesterol transport. This cholesterol efflux capacity is negatively correlated with severity of psoriasis leading to a deteriorated lipid profile with high values of LDL, triglycerides and low levels of HDL. Thus dyslipidemia become more frequent in psoriasis.[37]

Psoriasis is also associated with an increased hepatic inflammation, potentially via the excess production of TNF-α in the skin and serum. Observations on animal models had shown that chronic hepatic inflammation in subclinical inflammatory states, such as diabetes increased the synthesis and secretion of apo-B containing particles (LDL and VLDL) in the liver. A study done on University of Pennsylvania School of Medicine hypothesized that psoriasis being a chronic inflammatory disease would be associated with an impaired cholesterol efflux and abnormal lipoprotein particles profile. Furthermore, they have demonstrated that HDL dysfunction and impairment of reverse cholesterol transport (RCT) will occur in human inflammatory syndromes contributing to increased CVD risk.[38]

Psoriasis and cardiac status:

Nehal Mehta highlighted the strong evidence of connection between inflammatory state, psoriasis and cardiometabolic disease. A human endotoxemic model study in healthy human volunteers had revealed activation of innate immune pathways relevant to cardiometabolic disease such as peripheral IR, endothelial cell activation and impaired reverse cholesterol transport and characterized by increased cytokine signaling. These findings suggest a shared cytokines and inflammatory

mechanism between psoriasis and atherosclerosis favoring cardiovascular pathology. The inflammatory mediators from the skin are found to access the systemic circulation, then reach back to act on the subcutaneous fat and distant tissues resulting in interference of insulin signaling contributing to a metabolic state that favor cardiovascular pathology.[39]

A population based cohort study with UK electronic medical record data was the first study that evidenced an increase in cardiovascular risk in psoriasis patients. This is followed by many studies that reported a high risk of T2D, hypertension, hyperlipidemia, hypercholesterolemia and obesity. However, a cross-sectional study by KORA (Cooperative Health Research in the Region of Augsburg, Germany) showed that no statistically significant difference exists between BMI, blood pressure and total cholesterol to HDL cholesterol ratio. Statistically significant association is seen with waist circumference, T2D and MI. Thus psoriasis appears as an independent risk factor for T2D and MI.[40]

Psoriasis and type 2 DM:

Cohort studies at Boston had found an elevated risk of incident T2D among younger individuals with psoriasis. They suggested the probable link between psoriasis with IR and T2D could be inflammatory cytokines such as IL-6 and TNF and adipokines such as leptin and adiponectin. They concluded that immune-mediated inflammatory processes, metabolic biomarkers and environmental factors would form the connecting link between psoriasis and diabetes.[41]

A study on Danish population comparing the incidence rates of DM among normal and psoriasis patients had shown a significantly higher incidence of new onset DM irrespective of age and concomitant morbidity. Chronic inflammation associated with increase in tumor necrosis factor-α and insulin-like growth factor-II was found as a link between psoriasis and type 2 DM. Recent studies suggested an improvement of insulin sensitivity in psoriasis patients with the use of tumor necrosis factor-α antagonists which emphasized the overlap and sharing of disease mechanism between chronic inflammatory diseases and DM. Hence psoriasis patients are at increased risk of DM.[42]

A large multicenter study on T2D patients with psoriasis had revealed that the patients with both the diseases are disadvantaged as they have to manage two diseases. Their self-care on diabetes might be neglected despite requiring intense therapy. Insulin therapy was more frequently needed for treatment of these patients probably due to the association between inflammation and insulin resistance. The decrease in insulin sensitivity worsens the metabolic control so such patients should be encouraged to concentrate on their metabolic status and improve it by life style changes.[43]

Rahat S. Azfar had shown in his study that the risk of diabetes was increased amongst psoriasis patients in a dose dependent manner with the severity of illness. They had found psoriasis as an independent risk factor for incident diabetes. Hence psoriasis patients should be encouraged to undergo therapeutic lifestyle changes to lower their risk of diabetes and appropriate screenings for signs of insulin resistance.[44]

Psoriasis and obesity:

Psoriasis is a chronic auto-immune inflammatory skin disease expressing as skin plaques affecting mainly the scalp, back, elbows and knee, chronic plaque type being the most common form. The skin lesions of psoriasis being visible present early but MS has insidious changes and delayed symptoms with a high morbidity together with mortality. Studies of varying methodologies on association between these two will provide early opportunities for diagnosing and treating it.

Most of the Indian and international studies could not show a significant difference in BMI between psoriasis patients and controls. The mean BMI of psoriasis patients and controls in a hospital based case control study by Praveenkumar at Pondicherry medical college were 24.23 and 24.56 respectively. The mean waist circumference of psoriasis patients in this study was lesser than that of controls. Hence, we see that obesity is not an important component for MS in psoriasis patients of India.[45]

Insulin:

Insulin is a beautifully organized protein discovered by Frederick Banting and Charles Best during the year 1921 in Toronto. Following this great discovery and crystallization of insulin by John Jacob Abel in 1926, various laboratory studies were performed. C. R. Park and coworkers established the action of insulin in facilitating the transport of glucose via plasma membrane in tissues such as muscle. Research works had provided evidence on the direct action of insulin on liver in increasing the glycogen content, RNA synthesis, protein synthesis and also DNA

synthesis after 36 to 60 hours of insulin stimulation. Further studies indicated the action of insulin in the expression of genes encoding metabolic pathway regulating enzymes including those of glycolysis and gluconeogenesis. Insulin is also known to stimulate many anabolic processes.[46]

Secretion of insulin:

Insulin is synthesized, stored and secreted from the beta cells of the pancreatic islets. Insulin biosynthesis is encoded by insulin gene and regulated at transcriptional and translational levels. The synthesis begins with the formation of a 110 amino acid precursor called preproinsulin, which translocates across the rough endoplasmic reticulum membrane via a peptide conducting channel into the lumen. During this journey, the signal peptide is cleaved from preproinsulin by peptidase to yield proinsulin.

The proinsulin undergoes folding, disulphide bonds formation and maturation of three dimensional conformation. The proinsulin then gets transported to the golgi apparatus, enter the secretory vesicles and cleave to insulin and C-peptide. This insulin together with C-peptide and islet amyloid polypeptide are stored in secretory granules. Fusion of these secretory granules with the plasma membrane results in the release of insulin into the circulation. The insulin stored in the β cell granules are in a hexameric form and they get dissociated to monomeric forms in the circulation. 2D NMR studies have revealed these different forms of insulin and the native structure of insulin.[47]

Actions of Insulin:

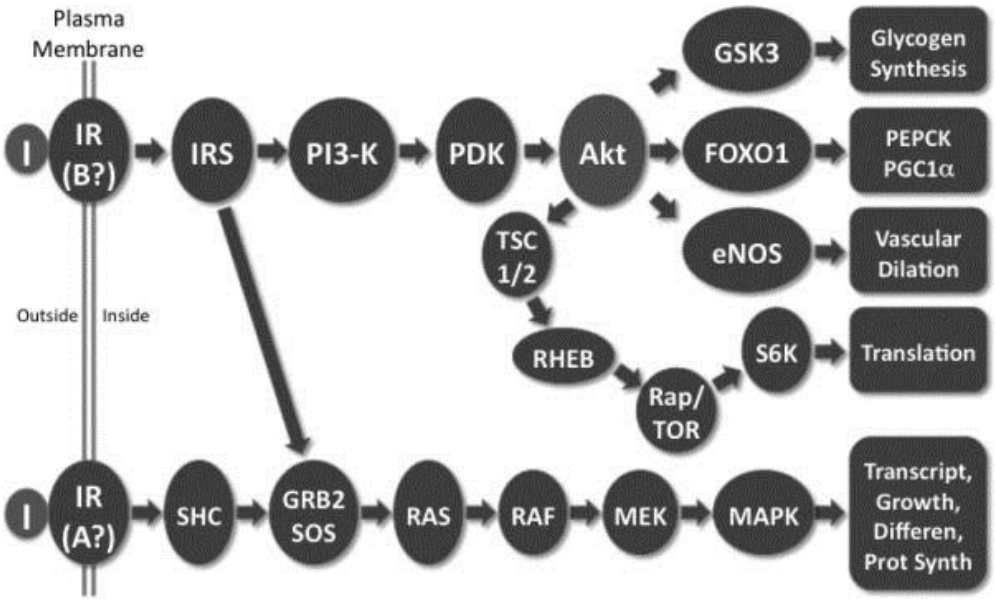
Insulin is secreted from islet β cells of pancreas following food intake. Insulin act on insulin receptors expressed on the skeletal muscle and adipose tissue and stimulate the glucose uptake in these cells through GLUT4 (glucose transporter). This uptake of glucose by skeletal muscle and adipose tissue serves to maintain glucose homeostasis by very low level of glucose uptake during basal condition and robustly activated glucose entry following food intake in response to insulin. This rapid glucose clearance is through insulin responsive glucose transporter GLUT4. In response to insulin, intracellular GLUT4 protein vesicles translocate to the plasma membrane, become a membrane spanning protein and facilitate the uptake of glucose. The interaction of these vesicles and SNARE proteins located at the plasma membrane favor this effect.[48]

Mechanisms of insulin action:

Insulin binds with the insulin receptors (IR-A or IR-B) present on the cell membrane and activates an intrinsic tyrosine protein kinase. This leads to autophosphorylation of receptors and activation of insulin signaling pathways. Insulin signaling pathways are of two types, a dominant pathway and an alternative pathway. The dominant pathway contains a family of proteins called Insulin Receptor Substrates which activate a cascade of serine protein kinases. A major branch point of this pathway is by Akt (protein kinase B) and its downstream substrates, which are involved in various physiological functions preferably on the regulation of fuel homeostasis. The alternate pathway is by ras/ MAP-kinase

activating the serine-protein kinase cascade. This pathway plays a role in the regulation of transcription, protein synthesis, cell growth and differentiation.[49]

Fig 1- Mechanisms of Insulin action.[49]



Akt is the main mediator of most of the metabolic effects of insulin, regulating glucose transport, glycogen synthesis, gluconeogenesis and lipid synthesis. The Shc-Grb2-Sos-Ras-Raf-MAPK pathway controls cellular proliferation and gene transcription.

Tyrosine phosphorylation causes activation of insulin receptors. Phosphorylation of serine and threonine causes shut down of insulin signal. Negative regulators of insulin action are cytoplasmic tyrosine phosphatases, transmembrane phosphatases and lipid phosphatases. The phosphatases dephosphorylate the tyrosine residues of insulin receptor complexes thus reducing their activity. This probes into the activity of rate limiting enzymes of glucose and

lipid metabolism such as glycogen synthase, hormone sensitive lipase and acetyl CoA carboxylase. Cyclic AMP and diacyl glycerol from lipids induces serine phosphorylation of insulin receptor complexes and impair insulin signaling.[50]

Studies in Akt2 knockout mice had highlighted the essential role of Akt2 in GLUT4 translocation. Akt signaling associated with downstream pathways like mTOR was found to be responsible for skeletal muscle protein synthesis and enhanced glycogen synthesis. There are evidences that mTOR activation increase the transport of aminoacids into the skeletal muscles. The whole body nutrient homeostasis is based on the nutrient handling capabilities of the skeletal muscle, adipose tissue and liver which are the insulin sensitive tissues.[51]

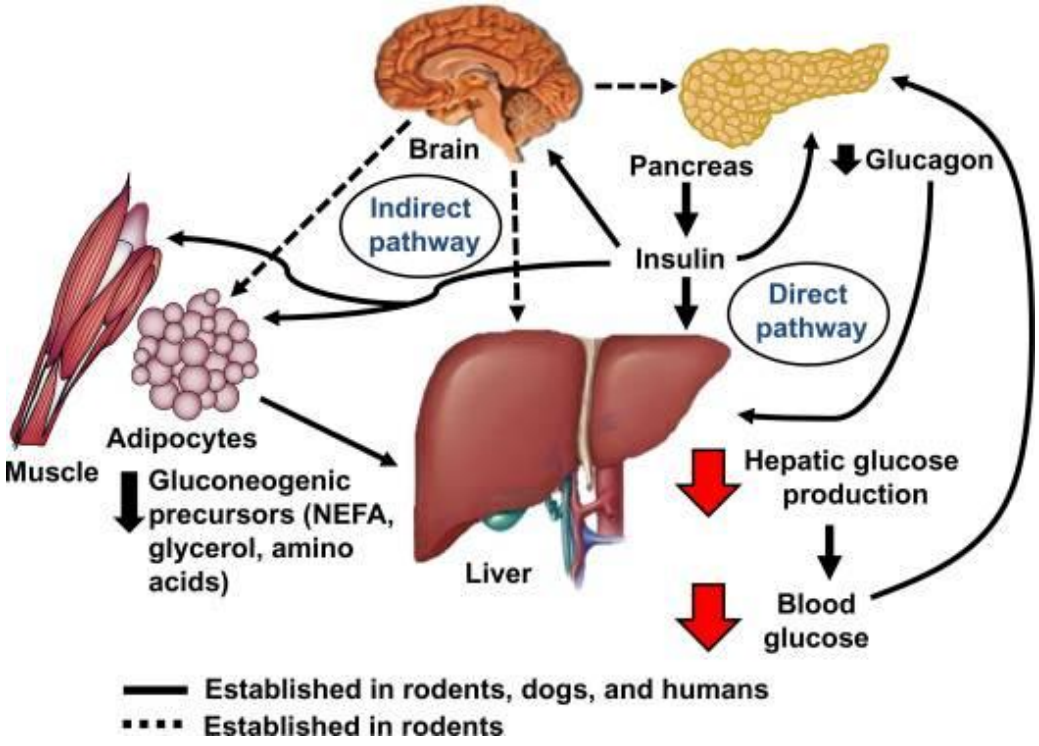
Action of insulin in liver:

In liver, insulin increases glycogen synthesis by stimulating glycogen synthase through Akt pathway. Insulin also suppresses glycogenolysis by acetylation, dephosphorylation and inactivation of glycogen phosphorylase. Insulin indirectly stimulates glucose uptake by stimulating the expression of glucokinase which phosphorylates glucose to glucose 6 phosphate. Glucose 6 phosphate is a precursor and an allosteric activator for glycogen synthesis and also allosterically inhibits glycogen phosphorylase. This can cause a further increase in liver glycogen levels.[52]

Insulin increases postprandial hepatic glucose utilization and suppresses hepatic glucose production. Insulin act on liver through direct and indirect pathways. The direct action is by binding with hepatic insulin receptors. 60% of secreted insulin is found bound with insulin receptors of hepatocytes. The phosphatidyl inositol 3-OH kinase pathway is activated resulting in Akt-directed phosphorylation of the transcription factor Forkhead box O1 (FoxO1). This causes termination of the transcription of two enzymes needed for gluconeogenesis, namely phosphoenol pyruvatecarboxykinase (PEPCK) and glucose-6-phosphatase (G-6-Pase).

Experiments on mice has shown that deletion of hepatocyte insulin receptors has caused activation of FoxO1 leading to unregulated glucose production and glucose intolerance. Studies also reveal indirect or extrahepatic regulation of hepatic glucose production done by insulin. The proposed mechanisms are suppression of glucagon secretion from pancreas, inhibition of lipolysis and proteolysis hence there is reduced availability of gluconeogenic precursors and finally control via central nervous system action. Thus, liver plays an important role in glucose homeostasis by increasing its consumption in postprandial state and production in fasting state. This hepatic glucose metabolism is impaired in diabetes.[53]

Fig 2 – Metabolic role of Insulin in various organs[53]



Insulin is a regulator of many metabolic functions of liver including cholesterol homeostasis. Insulin promotes lipogenesis, lipoprotein synthesis and VLDL secretion. Hence hepatic IR contribute to dyslipidemia.[54]

The stimulation of denovo lipogenesis in liver by insulin is through nuclear hormone LXR (liver X receptor). Knock down of LXR by antisense oligonucleotides in mice liver has proved the interaction of insulin and LXR in the regulation of lipogenic genes. Induction of LXR by insulin causes activation of the lipogenic enzymes like fatty acid synthase and stearoyl CoA desaturase and also lipogenic transcription factors namely sterol regulatory element-binding protein-1c and carbohydrate response element-binding protein. LXR is also found to play a

major role in activating the synthesis of unsaturated fatty acids, facilitating cholesterol efflux and hence reverse cholesterol transport. When there is insulin resistance, the lipogenic action of LXR induced by insulin is continued but the cholesterol efflux is decreased leading to fatty liver and increased triglycerides in circulation.[55]

Euglycemic hyperinsulinemic clamp technique studies in moderately obese individuals have explained that the lipolytic suppression effect of insulin in adipose tissue is by decreasing the activity of hormone sensitive lipase and adipose tissue triglyceride lipase resulting in decreased release of NEFA. Insulin also increases the triglyceride clearance by stimulating the activity of lipoprotein lipase. There is an acute inhibition of VLDL secretion following postprandial insulin spike.[56]

Action in heart:

Glucose metabolism in heart is 4-fold greater in cardiac muscle than skeletal muscle and they show a greater expression of the major insulin-responsive glucose transporter, GLUT4. Insulin signaling causes translocation of GLUT4 receptors from the intracellular pool to the cell surface and increases glucose uptake into the cells. Insulin has the same action on GLUT1 of cardiomyocytes to a lesser extent. GLUT4 and GLUT1 receptors account for 60% and 40% of total glucose carriers, respectively.

Insulin also activates the intracellular signaling proteins causing tyrosine phosphorylation of insulin receptor substrate (IRS), and activation of phosphatidyl-inositol-3 kinase (PI 3-kinase), Akt/protein kinase B (PKB), and protein kinase C.

The maintenance of glucose metabolism in necessary for normal cardiac function and abnormal function and cell death can occur when the cardiac ability to utilize glucose is impaired.[57]

IR affects cardiac function. There is decreased entry of glucose into the cell through GLUT-4 receptors and increase in fatty acid accumulation. There is increased expression of cardiac PPAR-α (peroxisome proliferator activated receptor alpha) resulting in enhancement of fatty acid uptake and oxidation. So the cardiac metabolism switches from glucose utilization to fatty acid oxidation. This in turn decreases cardiac efficiency.

Nitric oxide mediated coronary vasodilatation is also mediated by Akt pathway. IR in endothelial cells of heart produces impaired generation of nitric oxide leading to hypoxia and reduced angiogenesis. Endothelial insulin resistance causes an increased release of endothelin-1 (ET-1) which causes cardiac hypertrophy and fibrosis.[58]

Insulin resistance:

Insulin resistance is defined as disturbance in the biological action of insulin such as reduction in the insulin mediated glucose disposal and inhibition of hepatic glucose production. There is a failure in response of body cells to effectively use insulin. When this condition progresses, apoptosis of islets cells leads to DM. Since IR is a major predisposing factor in the occurrence and progression of DM, it is used as a screening index in the primary prevention of DM. Reaven proposed a model of DM progressed from IR.

Recent evidences have shown a non-obesity related correlation between IR and DM. According to WHO, IR is taken as a value greater than 75th percentile of that of non-diabetic subjects. HOMA-IR is found to be the most convenient and efficient way to measure IR using fasting plasma insulin and fasting plasma glucose.[59]

Measurement of IR:

IR is an independent risk factor and develops early in the pathological process of diabetes. There are evidences in many studies that IR predate the onset of the diabetes even by 10-20 years. Hence quantitative assessment of IR can be very useful before abnormal glucose tolerance or diabetes sets in. The quantitative measurement of the effect of insulin in relation to blood glucose level is termed as an index of insulin resistance.

A simple index of IR is defined as an index estimated from a fasting blood sample with or without other blood samples following no interventions such as intravenous administration of exogenous glucose or insulin. Such simple indices are convenient and easy, hence most commonly used for estimating IR. HOMA-IR and QUICKI are examples of these simple indices and they are based on fasting glucose and insulin. They assess hepatic IR more sensitively than peripheral insulin sensitivity. Hepatic IR is considered the major factor contributing to fasting hyperglycemia, impaired fasting glucose and pre-diabetic state. Peripheral tissue IR tends to develop at a later stage but there is a correlation between hepatic and peripheral IR.[60]

QUICKI (quantitative insulin sensitivity check index) is one of the classical insulin resistance indices which was once found to be the most accurate and useful index for determining insulin sensitivity in humans. However, QUICKI and insulin action are not correlating in individuals with mild insulin resistance or in impaired glucose tolerance stage. Hence QUICKI is less robust in diagnosing IR early before T2DM or MS sets in.

IR is the root factor for T2DM. It is the most unifying parameter which characterizes the pathophysiology of MS. Though MS is found to drive into T2DM and cardiovascular disease, T2DM is independently associated with higher risk of cardiovascular disease which is further aggravated by MS factors. Adiponectin and resistin are thought to bridge T2DM and MS with cardiovascular risk.[61]

A one year follow up study on 2642 Japanese workers has found a cause-effect relationship between IR and MS. This study evaluated the insulin related biomarkers such as HOMA-IR (Homeostasis Model Assessment for Insulin Resistance) and QUICKI (Quantitative Insulin Sensitivity Check Index). HOMA-IR and QUICKI are calculated as follows:

$$HOMA - IR = (FPG\ in\ mg/dl \times insulin\ in\ mIU/L)/405$$

$$QUICKI = 1/[common\ logarithms\ (FPG \times insulin)]$$

Although fasting plasma glucose is used, contributions of glucose level to these calculations are relatively small. WHO defines IR as HOMA-IR values ≥ 1.8, but for this Japanese study, HOMA-IR ≥ 2.5 is considered as a significant factor for the

development of MS. But this HOMA-IR and QUICKI are applicable only with fasting blood sugar levels less than 140 mg/dl. [62]

McLaughlin et al., has identified the lipid ratio TG/HDL-C as another means of identifying IR with a sensitivity 79% and specificity 85%. They proposed a cut-off value of ≥ 3.5 as a predictor of IR.A study done at the Cardiology department of Medical College & Hospital, Kolkata on acute coronary syndrome patients from April 2011 to March 2012 have found that TG/HDL-C ratio has a higher screening ability and sensitivity to identify IR when compared to TC/HDL-C ratio.

Significant association between TG/HDL-C and IR had been reported by Brehm et al. But recent data suggest that IR is an independent predictor of cardiovascular disease irrespective of hypertension, obesity or dyslipidemia. Yet, plasma total cholesterol, triglycerides and HDL-C were independently associated with insulin levels and hence IR.[63]

Metabolic derangements due to IR:

IR in several tissues such as liver, muscle, adipose tissue, vascular tissue and neuronal tissue can drive into hyperinsulinemia. The six major pathways that are disrupted in metabolic diseases (i.e. obesity, metabolic syndrome, and Type 2 diabetes) are impaired hepatic glucose uptake and glycogen deposition, activated gluconeogenesis and de novo lipogenesis, accelerated fatty acid delivery and triglyceride esterification.

Liver is the major organ that handles a greater proportion of dietary nutrients during the 24 hour feed-fast cycle. In the fasting state, IR is associated with

inability of insulin to restrain hepatic glucose production resulting in inappropriately high levels of glucose production by increase in gluconeogenesis and glycogenolysis. Also the insulin mediated glucose uptake in muscle cannot be augmented resulting in hyperglycemia.

The liver normally switches its function following a carbohydrate meal from production to net consumption of glucose. It stores a substantial amount of glucose as glycogen which can be released in the post-absorptive state by glycogenolysis. The concentrations of glucose and insulin together determine the magnitude of this hepatic glucose uptake. But during IR, the liver fails to get switched off following a meal from production of glucose to its consumption. The insulin can neither suppress hepatic glucose production nor augment glucose uptake in the liver contributing to exaggerated hyperglycemia. But this IR is so selective, that there is augmented hepatic lipogenesis and triglyceride accumulation.

Although glucose uptake in the brain is not generally regulated by insulin, specific areas in brain exhibit IR ad modify the neural circuits that regulate the response of liver and peripheral tissues to insulin thereby exacerbating impaired glucose metabolism.

In addition, there is impaired suppression of glucagon secretion from the pancreas as well as adipose tissue lipolysis. These extrahepatic factors exacerbate the ineffectiveness of insulin to suppress hepatic glucose production and enhance liver glucose uptake.[64]

Insulin normally acts as an anti-lipolytic hormone in adipose tissue and it suppresses the release of stored fatty acids by decreasing the activity of hormone sensitive lipase. In conditions of IR in fat cells, higher levels of free fatty acids leave the fat cells and reach the circulation to be taken up by liver and skeletal muscles which cannot safely store large amounts of fat. There is a paradoxical activation of lipoprotein lipase in hyperinsulinemia which hydrolyzes lipoprotein triglycerides at the surface of fat cells to release free fatty acids. The excess fat released into the blood stream and sequestered by other organs mark the beginning of lipotoxicity. The progress of chronic diseases associated with IR becomes accelerated with increased lipotoxicity. Thus IR has to be categorized as a metabolic dysfunction and keeping insulin within a therapeutic zone is vital for survival.[65]

Inflammation and IR:

There is a potential role of inflammatory cells in mediating IR. Studies had demonstrated role of macrophages, CD4 and CD8 lymphocytes in developing IR. The cytokines secreted by the T cells directly impair the action of insulin in target tissues. In vitro studies had shown evidences that increase in interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) could induce IR. Tracey McLaughlin in his studies had concluded that CD4 cells, CD8 cells and T-helper cells are highly associated with systemic inflammation and IR. [66]

Inflammation is a mechanism of defense that protects and also helps to recover the body from infections or any insults. The relative balances between

proinflammatory and anti-inflammatory immune cells have a tight control over the process of inflammation. Dysregulation of inflammation had been implicated as a major cause of many autoimmune diseases. In vitro studies have shown that pro-inflammatory cytokine TNFα lowers the level of insulin signaling components, induce the phosphorylation and hence inhibition of IRS thereby inhibits insulin signaling.

The linear signaling cascade following insulin binding to its receptor and resulting in Akt activation is disrupted in insulin resistance. This impairment chiefly affects the insulin responsive cells such as adipocytes, myocytes, hepatocytes and β-cells interfering with the translocation of GLUT4 and synthesis of glycogen. Adipose tissue and muscle are similarly affected where IR present as inability of glucose disposal. This is compensated by secretion of more insulin by pancreatic β-cells. However the β-cells fail when the limit of their secretory capacity is crossed. The inappropriately low level secretion of insulin in response to a definite concentration of glucose leads to T2D.[67]

IR and diabetes:

Diabetes itself is a group of metabolic diseases having high blood sugar values either due to insufficiency of insulin production or impairment in biological response to insulin, the second one being considered as IR. T2DM is characterized by IR and hyperglycemia. IR is considered as the salient feature of T2DM. IR also contribute to beta cell failure evidenced by observing apoptosis of beta cells following elevated glucose concentrations in cultured islet cells from diabetes-

prone Psammomys obesus. There are evidences that insulin is uniquely secreted by beta-cells and has anti-apoptotic role via PI3K/Akt pathway thereby protecting the beta cells. The beta cell mass is maintained by a dynamic process of balance in replication and apoptosis. In IR, beta cell failure sets in.

Blood glucose homeostasis is crucially maintained by the arrival and localization of GLUT4 in the plasma membrane of muscle and adipose tissue with subsequent cellular glucose influx. This normal metabolic process of glucose uptake in skeletal muscle and adipose tissue are impaired in IR. Thus IR had become the initiating mechanism in the pathogenesis of T2DM consequently leading to glucose toxicity.[68]

Diabetes is the final stage of the pathogenic process that start as IR with increased strain on beta cells of pancreas, progressing through prediabetes stage with impaired ability to control blood sugar and reaching into full blown diabetes with death of beta cells and inability to control fluctuations of blood sugar with natural insulin. IR is compensated for a time period by its increased production by putting considerable strain on beta cells. By the time diabetes occur, 80% of beta cells were lost. IR along with its predisposition to diabetes is also associated with early cardiovascular morbidity and other complications. So at the stage of prediabetes itself, untreated patients will be entering into the very high risk of full-blown diabetes, cardiovascular events and other complications.

ADA had proposed diagnostic criteria for prediabetes as follows:

Impaired glucose tolerance - as 140 to 200 mg/dL 2-hour post load glucose level following oral glucose tolerance test (OGTT),

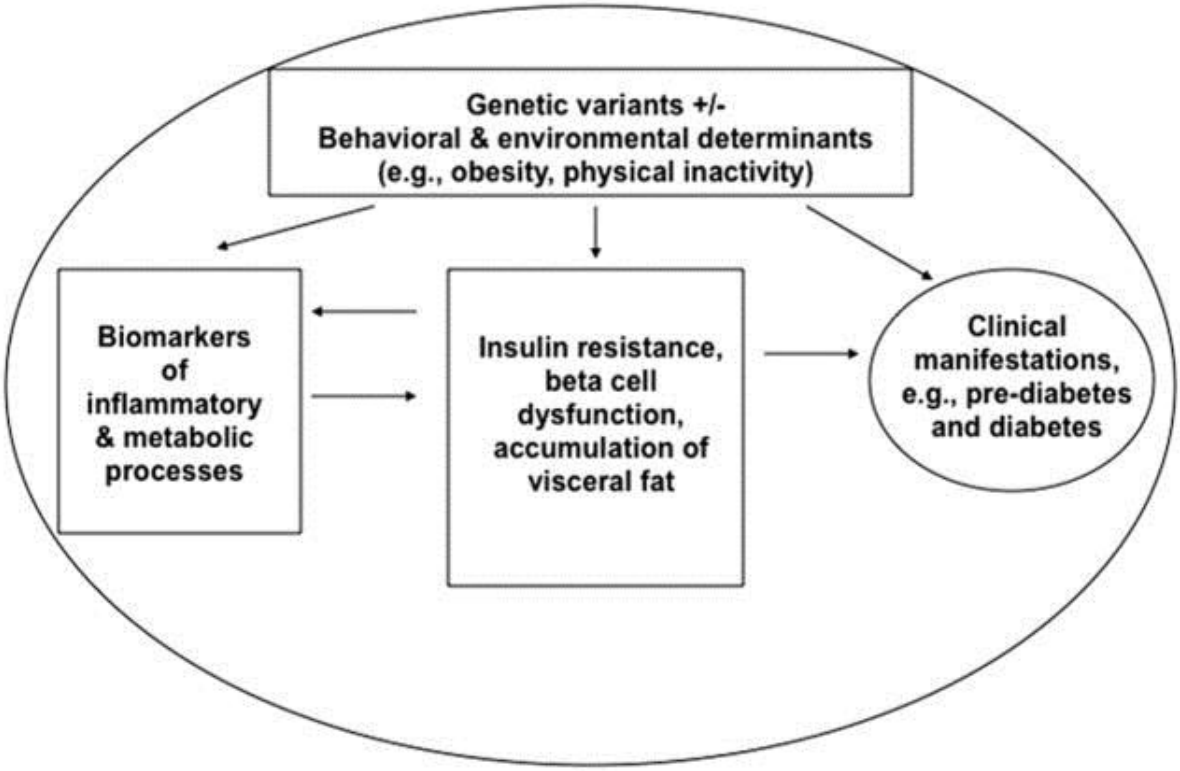
Impaired fasting glucose - as 100 to 125 mg/dL of fasting glucose levels orA1C (glycated hemogloblin) level at 5.7% to 6.4%.

The above criteria can only identify prediabetes, the stage of inability to control blood sugar within normal limits exercising beta cells to IR. Thus though the above tests are cheaper, there is a great need for diagnostic tests to identify early signs of IR. The battle against diabetes can be won only by identifying and aggressively treating the root cause IR.[69]

Maintenance of glucose tolerance within normal physiological limits by complex feedback mechanism is called glucose homeostasis. The direct measures of glucose homeostasis are euglycemic clamp and frequently sampled intravenous glucose tolerance test. Their indirect measures are fasting insulin and fasting glucose. These measures indicate IR and β cell response.

Aberrant glucose homeostasis contributes to IR, where there is inappropriate use of insulin by muscle, fat and liver. Hence more insulin is required for the use of same amount of glucose. But as IR goes on increasing, the circulatory levels of glucose will also shoot up resulting in hyperglycemia contributing to T2DM.When insulin secreting capacity is decreased, established T2DM had set in. So the secretory capacity cannot be used as a predictor of T2DM and increased IR is taken

into account as measures of β cell function in prediabetic subjects. This concept is termed as Disposition Index.[70]



Disposition Index is the product of acute insulin response and insulin sensitivity following an intravenous glucose tolerance test. In vitro studies in mouse and human islet cells have revealed that elevated circulating free fatty acids suppress the expression of transcription factors in β cells. So there is an impaired ability of β cells to sense glucose and secrete appropriate insulin. Thus the ability of β cells to compensate for low insulin sensitivity is impeded. This β cells compensation of IR can be measured using Disposition Index.[71]

International Obesity Task Force criteria for Asian populations has defined obesity and overweight as ≥25 kg/m^2 and ≥23 kg/m^2 respectively. Impaired Glucose Tolerance (IGT) and T2DM are associated with increase in insulin resistance (IR).

T2DM is the result of beta cell exhaustion following IR. The pancreas compensates to increasing IR until beta cell failure supervenes. IR was also said to be related to body fat.[72]

India possess a major contribution to the global health burden in diabetes The World Health Organization (WHO) and International Diabetes Federation (IDF) have reported a prevalence rates of diabetes is between 2.8% and 5.1% in individuals ≥20 years of age. In India, the National Urban Diabetes Survey conducted at six major cities, revealed 12% prevalence rates of diabetes and 14% impaired glucose tolerance. With an increase in population size and rate of disease India is expected to have an estimated prevalence of 80 million diabetics by 2030, and this accounts for one-fifth of world diabetics.

Asian Indians have a higher risk of Type 2 diabetes and premature coronary artery disease when compared to Europeans. This is related to a higher frequency of hyperinsulinemia, insulin resistance, dyslipidemia specially low HDL cholesterol and increased visceral fat, the features collectively referred to as the 'Asian Indian Phenotype or Paradox'.

Epidemiologic studies also show a strong role for genetics as evidenced by an increased risk for Type 2 diabetes and impaired glucose tolerance (IGT) in persons with positive family history. The etiology of Type 2 diabetes though not yet fully understood, it is likely that genes and environmental components play a major role in pathophysiology.[73]

Statistics reveal that India is expected to have 79.4 million people with diabetes by 2030 and carry the largest cardiovascular disease burden of the world. There is an increased prevalence of diabetes in South India specially a consistent escalation in younger population from 25.0 to 35.7% during the period of 2000 to 2007. These people are relatively low in birth weight and have hyperinsulinemia together with higher concentration of nonesterified fatty acids during fasting.[74]

IR and dyslipidemia:

Indians are relatively more Insulin Resistant probably due to the higher abdominal obesity. Adipocytokines are synthesized and secreted by adipocytes, they include adiponectin, resistin, leptin, TNF-α and IL-6. These factors play an important role in development of IR. IR is compensated by hyperinsulinemia. Hyperinsulinemia accelerates hepatic VLDL synthesis contributing to increased triglyceride levels. Also hyperinsulinemia stimulate sympathetic nervous system, proliferation of smooth muscle cells of blood vessels and increases sodium absorption contributing to hypertension.[75]

Studies done at Chinese and Flemish people have found that insulin resistance increased with increase in triglycerides and decrease in high density lipoprotein. The studies were conducted in association with Helsinke Declaration for investigation. IR was computed by HOMA-IR, also by C-peptide in diabetics and by insulin in non-diabetics. LDL cholesterol was calculated via Friedewald formula using serum HDL, triglycerides and total cholesterol. They found a close relation between lipoprotein metabolism, circulating level of triglycerides and HDL

cholesterol and it is disturbed in diabetic and IR patients. Dyslipidemia and inflammation are chaperones to IR. Their study implies that lowering of serum triglycerides, increasing HDL levels and controlling inflammation should be the main targets for prevention or treatment of IR.[76]

Gerald Reaven (Stanford, CA) had discussed the interrelation among hyperinsulinemia, hypertension, and cardiovascular disease. Reaven had found association of IR with elevated levels of BMI, fasting glucose, insulin, and triglyceride levels and low HDL cholesterol levels in a study on Italian population and hence he suggested that people with insulin resistance are in the group who has all the cardiovascular risk factors. This IR lipid pattern of elevated triglycerides and low HDL cholesterol was associated with increased CVD risk.[77]

IR and cardiac status:

IR is associated with impaired fibrinolysis characterized by hypercoagulability with elevation of fibrinogen and plasminogen activator inhibitor (PAI)-1. Hence IR becomes a prothrombotic state leading to a higher risk of cardiovascular events.[78]

Insulin increases fatty acid uptake by the heart but inhibits its utilization for energy. Insulin stimulates the uptake and oxidation of glucose by the cardiac muscle. Therefore insulin resistance causes a reduction in energy supply to the myocardium and a change in substrate utilization from glucose towards fatty acids. Thus IR become a central part of MS, the pathophysiology being associated with pro-inflammatory, prothrombotic and oxidative state predisposing to atherosclerotic

cardiovascular disease. The data of EPIPorto cohort study, Portugal showed that diastolic dysfunction of the heart deteriorates with IR and it predicts the future onset of heart failure.[79]

IR and MS:

MS is nothing but the constellation of factors including impaired glucose tolerance, low high density lipoproteins and high triglycerides predisposing the individual to increased risk of diabetes and cardiovascular illness. It has a complex pathogenesis and helps as a useful tool to identify the people who are at increased risk of diabetes and coronary illness. Ramchandran et al., has reported a 41% prevalence of MS in urban area of Chennai on the basis of modified ATP-III criteria. Prevalence of MS is found to be high among Indians. [80]

The term MS refers to a group of conditions including obesity, hyperlipidemia, high blood pressure and IR. MS can present in different forms but IR is suspected to form a common pathophysiological link between MS and its etiological components. The risk of developing all the abnormalities of MS is found to be strongly associated with IR.[81]

The health problems type 2 diabetes (T2D), and cardiovascular diseases (CVDs) are often preceded by the abnormalities such as obesity, insulin resistance, impaired glucose tolerance, dyslipidemia and high blood pressure together collectively called as MS. The abnormalities that are usually estimated for the diagnosis of MS include central obesity, triglycerides, high-density lipoprotein and fasting plasma glucose. Though the pathophysiology of MS is complex, majority of

patients had IR. MS not only leads to a high risk of type 2 diabetes, coronary or peripheral atherosclerosis and cardiovascular disease but also associated with some other systemic complications such as fatty liver disease, respiratory disease, and cancer.[82]

IR is a characteristic finding in MS. The progression of IR to T2DM happens only with exhaustion of beta cells. But the other compensations for hyperinsulinemia progresses before T2DM appear. A study on South Asians and Europeans had found a clear trend of higher IR in the order starting from no MS/ no T2DM, MS/ no T2DM to MS/ T2DM supporting their assessment that many people with IR may not develop T2DM. Their study also showed that South Asians are more vulnerable to chronic diseases such as MS and T2DM as they are predisposed to IR, dyslipidemia and beta-cell dysfunction at an earlier age.[83]

A SMART study at Netherlands used HOMA-IR to quantify IR to investigate the association of IR with occurrence of metabolic disturbances and cardiovascular abnormalities. HOMA-IR was taken for quantitative estimation of degree of IR. The extent to which HOMA-IR is related to each component of MS was evaluated in relation to ATP III criteria.

The relation between IR and components of MS based on this study is as follows:

MS components	IR
0	1.4 ± 0.7
1	1.8 ± 1.2
2	2.4 ± 1.5
3	3.1 ± 1.8
4	4.0 ± 2.6
5	5.6 ± 3.6

ATPIII criteria defined MS as having 3 of the metabolic abnormalities. They had found that IR is a major driver underlying the pathophysiology of MS and associated with increased cardiovascular risk and mortality.[84]

HOMA-IR is a surrogate method for estimating IR in epidemiologic or clinical setting. The cut-off values of HOMA-IR vary according to ethnicity and metabolic conditions of populations studied and defined by percentiles criteria. The optimal cut-off values of HOMA-IR to take into account as MS as per ATPIII range from 2.07 at 50 years and 2.47 at 70 years. The optimal cut-off suggested by IDF for MS was 2.05. In Spain, the threshold had dropped from 3.46 to 2.05 considering MS components.[85]

Various studies have taken value of HOMA-IR as 2.5 to indicate IR in adults. The same value is also found to provide maximum sensitivity and specificity in diagnosing MS in adolescence of both genders as per ATP III and IDF criteria.[86]

Psoriasis and IR:

Psoriasis is a T- cell mediated disease having increased Th type1 proinflammatory cytokines performing wide range of actions on insulin signaling, lipid metabolism and adipogenesis. Several studies had found a high risk of diabetes in psoriasis patients with IR as the probable link. IR was found even in non-obese patients and said to be in correlation with psoriasis index severity area. The inflammatory mediators involved in IR are disturbed in psoriasis. The inflammatory molecules produced in psoriasis skin including TNF, VEGF, interferon-γ and interleukins are released into the circulation depending on the severity and extent of skin lesion.[87]

A significant decrease in HOMA-IR was seen with a decrease in PASI. A prospective cohort study at Turkey had found IR in psoriasis patients, but their sample size is less taking 35 patients, hence the difference in IR found between patients and controls were not statistically significant. But the adipokine levels of psoriasis patients were similar to that of in prediabetic individuals supporting the association with IR. [88]

Psoriasis is associated with increased oxidative stress with decreased antioxidant capacity. The systemic inflammatory burden in psoriasis contributes to

IR. IR results in a state of shifted equilibrium of balanced proatherogenic and antiatherogenic effects towards predominant proatherogenic effects.[89]

The pathology of MS could be characterized by peripheral insulin resistance. MS is associated with IR and according to a study by Wilson et al., MS promotes the occurrence of T2D. Studies by Shoelson et al., Kalupahana et al., and Stienstra et al., have revealed a strong relationship between chronic low-grade inflammation and insulin resistance where pro-inflammatory cytokines such as interleukin-1β, interleukin-6 play a connecting role. It has been recognized that a pro-inflammatory state contributes to disease development and progression. In support of such a relationship is the observation that metabolic and immune response pathways are evolutionarily integrated and partly overlapping, and it is clear that the immune system plays a role in the development of metabolic diseases.

There is a close link between inflammation and metabolic disease, but the responsible mechanisms remain elusive. Skeletal muscles account for the major part of insulin induced glucose uptake but there is ignorance regarding the link between inflammation and IR in skeletal muscle. A closer examination had revealed presence of upregulated inflammatory genes such as histone deacetylase 9 (HDAC9), interleukin 6 receptor (IL6R) and CD97 molecule (CD97) in skeletal muscles which might play an important role in development of IR.[90]

Balato N and colleagues hypothesized in their study that the inflammatory mediators of autoimmune reactions in psoriatic march caused IR and this contributed to comorbidities such as diabetes and hypertension. Their data

confirmed this association. Also their findings supported the synergistic effects of chronic inflammations due to obesity and psoriasis, the concept put forward by Hamminga et al .[91]

Based on recent advances, it was found that both psoriasis and atherosclerosis are characterized by acceleration of immunological activity of helper T cells of type 1 and represent an ongoing systemic inflammatory state. Studies are now pointing towards IR as playing a primary role in forming a common association. This holds true even for psoriasis of mild severity and is independent of obesity. Insulin resistance state is proposed to be diminished by therapeutic interventions with methotrexate and tumor necrosis factor α antagonists.[92]

Thus though psoriasis is considered a chronic, T-cell mediated inflammatory disease chiefly affecting the skin and joints, several observational studies have demonstrated an association between psoriasis and systemic disorders eventually linked by elevated cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α). So there are recommendations to upgrade psoriasis to a systemic disease.[93]

Psoriasis is also a risk factor for development of abdominal obesity, hypertension and dyslipidemia. The inflammation pathogenic to psoriasis also develops atherosclerotic and metabolic disorders and vice versa. So a dermatologist is also responsible for diagnosing and monitoring these concomitant disorders. A

study had revealed that there is no difference in prevalence of insulin resistance and abnormalities of lipids between psoriatic patients and Polish citizens.[94]

Asians have a higher predisposition to obesity, MS, DM and cardiovascular disorders when compared to western population. There is a scarcity of literature highlighting the association of psoriasis with these morbidities. Comorbidities are multigenic, multifactorial timely unrelated secondary diseases involving same or other organs. This occurs in psoriasis. A higher prevalence of MS is seen in Indians and psoriasis represents an additional route for morbidity due to its positive correlation with IR. A study conducted at Department of Dermatology, Topiwala National Medical College and B.Y.L Nair Charitable Hospital, Mumbai have found a significant association between psoriasis and diabetes with odd's ratio 2.63 of abnormal glucose homeostasis in psoriasis. But IR did not appear to be related to duration or severity of psoriasis. They had suggested that further studies have to be carried out using large sample size.[95]

The prevalence of comorbidities in psoriasis is relatively low, hence large sample sizes are required to attain sufficient power in testing the associations. The observational studies can generate hypotheses, but cannot easily generate results that differentiate clearly between association and causality. The likelihood of a causal relation increases when a clear biological explanation is found for the association, confirmed by multiple studies with a dose-response relationship between exposure and outcome. The increased inflammatory status in psoriasis patients associated with higher levels of the multifunctional cytokine tumor necrosis

factor-α is proposed as the biological explanation found in association between psoriasis and several comorbidities.[96]

MATERIALS AND METHODS

SOURCES OF DATA

Psoriasis patients who attended the skin outpatient department of Sree Mookambika Institute of Medical Sciences, Kulasekharam, Tamilnadu and healthy age matched controls formed the subjects for the present comparative study. A total of 200 subjects which included 100 psoriasis patients and 100 normal persons, who came to the hospital during the time period of April 2016 to March 2017 were enrolled in the study.

INCLUSION CRITERIA

(1) All patients diagnosed with psoriasis attending skin outpatient department of Sree Mookambika Institute of Medical Sciences during the study period.

(2) Age between 18 to 60 years.

(3) Bystanders of patients attending various departments of Sree Mookambika Institute of Medical Sciences were taken for comparison.

EXCLUSION CRITERIA

(1) Patients with the following ailments were excluded:

Known diabetic patients,

Patients with known cardiovascular disease,

Patients with known chronic kidney disease,

Severely ill patients,

Patients taking systemic steroids or cyclosporine.

(2) Subjects not willing to participate.

METHOD OF COLLECTION OF DATA

Informed consents were obtained from the subjects after explaining about the study. The data was collected using a prestructured proforma. Baseline data including age, gender, occupation, detailed medical history including number of relapses, clinical examinations and relevant investigations were included as part of methodology.

The following parameters were collected: age, gender, blood pressure, height, weight and biochemical parameters. Blood pressure was recorded in sitting position in the left arm using the mercury sphygmomanometer (Diamond Deluxe BP apparatus, Pune, India). Two readings were taken 5 minutes apart and the mean of the two were taken as blood pressure. The standing height and weight were measured using stadiometer and digital weigh scale respectively. The Body Mass Index (BMI) was calculated as the weight of the body in kilograms to the square of the height in meters.

$$\text{Body mass index} = \text{Weight (Kg)} / \text{Height } \{m^2\}$$

Blood samples (5 ml) were collected employing standard infection prevention procedures from each participant after an overnight fasting of 12 hours. 2ml of blood was transferred to a fluoride vacutainer for fasting plasma glucose estimation and 3 ml of blood was transferred to a vacutainer containing clot activator. The serum was separated by centrifuging the blood in clot activator tube at 2500 rpm for 10 minutes. The plasma was separated by centrifuging the blood in fluoride vacutainer at 3500 rpm for 15 minutes. The samples were then used to determine the concentration of glucose, HDL cholesterol, triglyceride, and serum insulin.

1. ESTIMATION OF INSULIN

Serum insulin level was estimated by immuno-enzymatic sandwich assay using Beckman Coulter Access 2 Immunoassay Systems

PRINCIPLE

The Access Ultrasensitive Insulin assay is an immuno-enzymatic sandwich assay. The serum sample is added to a reaction vessel along with mouse monoclonal anti-insulin alkaline phosphate conjugate and paramagnetic particles coated with mouse monoclonal anti-insulin antibody.[97]After incubation, the bound materials are held in a magnetic field and the unbound materials are washed away. Then the chemiluminescent substrate Lumi-Phos 530 is added to the vessel and the light generated by the reaction is measured with a luminometer. The intensity of

light production is proportional to the concentration of insulin in the sample. The amount of analyte is determined from a multipoint calibration curve.

REAGENTS

Reagent 1a	Mouse monoclonal anti-insulin coupled to paramagnetic particles, TRIS buffer, bovine serum albumin matrix.
Reagent 1 b	Mouse monoclonal anti-insulin conjugated to bovine alkaline phosphatase, TRIS buffer, BSA matrix.
Reagent 1 c	Mouse IgG in HEPES buffer, BSA matrix.

PROCEDURE

The assay was done using Beckman Coulter Access 2. The reagent packs were loaded in the instrument. 20 µL of sample was used up for each assay. The results in µIU/mLwere displayed at the appropriate screen.

REFERENCE RANGE

Normal Range	Units
1.9-23	µIU/mL
13.0-161	pmol/L

2. ESTIMATION OF BLOOD GLUCOSE

Blood glucose was estimated by hexokinase glucose-6-phosphate dehydrogenase method.

PRINCIPLE

Glucose is phosphorylated to glucose-6-phosphate by hexokinase enzyme in the presence of adenosine tri phosphate and magnesium ions. Glucose-6-phosphate is oxidized to 6-phosphogluconate by glucose-6-phosphate dehydrogenase. During this reaction NAD^+ (nicotinamide adenine dinucleotide) is reduced to NADH (reduced nicotinamide adenine dinucleotide). The change in absorbance measured at 340/380 nm is proportional to the amount of glucose in the sample.

REAGENTS

Reagents	Concentration
PIPES- buffer (pH7.6)	24.0 mmol/L
NAD^+	≥ 1.32 mmol/L
Hexokinase	≥ 0.59 KU/L
ATP	≥ 2 mmol/L
Mg^{2+}	2.37 mmol/L
G6P-DH	≥1.58 KU/L

PROCEDURE

After making entry of patient details, the sample of plasma was introduced into Beckman Coulter AU 480. The results displayed were recorded in mg/dl. The values can be multiplied by 0.0555 for mmol/L.

REFERENCE VALUE

Adult	70 – 105 mg/dL

3. CALCULATION OF INSULIN RESISTANCE

Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) defines Insulin Resistance. HOMA-IR was calculated using the fasting plasma glucose levels and fasting serum insulin levels. The product of fasting plasma glucose in mg/dl and fasting serum insulin in mIU/L is divided by 405 to obtain the values of HOMA-IR.

$$\text{HOMA-IR} = (\text{FPG in mg/dl} \times \text{insulin in mIU/L})/405$$

The HOMA-IR values equal to or greater than 2.5 is taken as IR.[98]

4. ESTIMATION OF SERUM TRIGLYCERIDES

PRINCIPLE

The triglycerides present in the serum are hydrolyzed by lipases to glycerol and fatty acids. Glycerol is phosphorylated to glycerol -3-phosphate by adenosine tri phosphate in the presence of glycerol kinase. The glycerol -3-phosphate is then

oxidized to form hydrogen peroxide and dihydroxyacetone phosphate in the presence of glycerol phosphate oxidase. The hydrogen peroxide formed reacts with 4-aminophenazone and N,N-bis-3,5-dimethylaniline, disodium salt (MADB) in the presence of peroxidase and produce a chromophore which is read at 660/800nm. The increase in absorbance is proportional to the triglyceride content of the sample.

REAGENTS

PIPES buffer (pH 7.5)	50 mmol/L
Lipase (Pseudomonas)	≥ 1.5 kU/L (25 μkat/L)
Glycerol kinase	≥ 0.5 kU/L (8.3 μkat/L)
Glycerol phosphate oxidase	≥ 1.5 kU/L (25 μkat/L)
Ascorbate oxidase	≥ 1.5 kU/L (25 μkat/L)
Peroxidase	≥ 0.98 kU/L (16.3 μkat/L)
ATP	1.4mmol/L
4-Aminoantipyrine	0.50mmol/L
Magnesium acetate	4.6 mmol/L
MADB	0.25mmol/L

PROCEDURE

After making data entry, the sample was introduced into Beckman Coulter AU 480. The result displayed at the appropriate screen is registered.

REFERENCE RANGE

Serum Triglyceride	Risk Classification
<150 mg/dL	Normal
150-199 mg/dL	Borderline High
200-499 mg/dL	High
≥500 mg/dL	Very High

4. ESTIMATION OF HIGH DENSITY LIPOPROTEINS

Selective measurement of HDL cholesterol was done using two reagent homogenous system.

PRINCIPLE

The assay of HDL cholesterol is composed of two distinct phases. In phase 1, cholesterol present in non-HDL-lipoproteins are solubilized by cholesterol oxidase, peroxidase and DSBmt (N,N-bis-m-toluidine disodium) to generate a

colorless product. In phase 2, an unique detergent selectively solubilizes HDL-lipoproteins. The HDL cholesterol released react with cholesterol esterase, cholesterol oxidase and a chromogen system to yield a blue colored complex which is measured bichromatically at 600/700nm. The increase in absorbance is proportional to the HDL concentration in the sample.

REAGENTS

Goods Buffer (pH 6.0)	
Cholesterol esterase (Pseudomonas)	375 U/L
Cholesterol oxidase (E.coli)	750 U//L
Peroxidase (Horseradish)	975U/L
Ascorbate oxidase (Curcubita sp,)	2250U/L
DSBmT	0.75mmol/L
4-aminoantipyrine	0.25mmol/L

REFERENCE VALUES

Adults	23-92 mg/dl

A value of less than 40 mg/dL is indicative of a major risk factor for coronary heart disease.

STATISTICAL ANALYSIS

Data collected were entered in the excel sheet. Analysis was done by SPSS version 20. Percentage, mean and standard deviation were calculated. Independent sample “t” tests were done for comparison of variables in two groups. The p values of < 0.05 were considered as statistically significant.

RESULTS

The present study was undertaken to evaluate the presence of insulin resistance in psoriasis patients and the association of alterations in parameters like fasting plasma glucose, serum high density lipoproteins and serum triglycerides in these patients. The study population was 200, of which 100 are psoriatic patients and 100 are healthy age matched controls.

GENERAL CHARACTERISTICS OF THE STUDY POPULATION

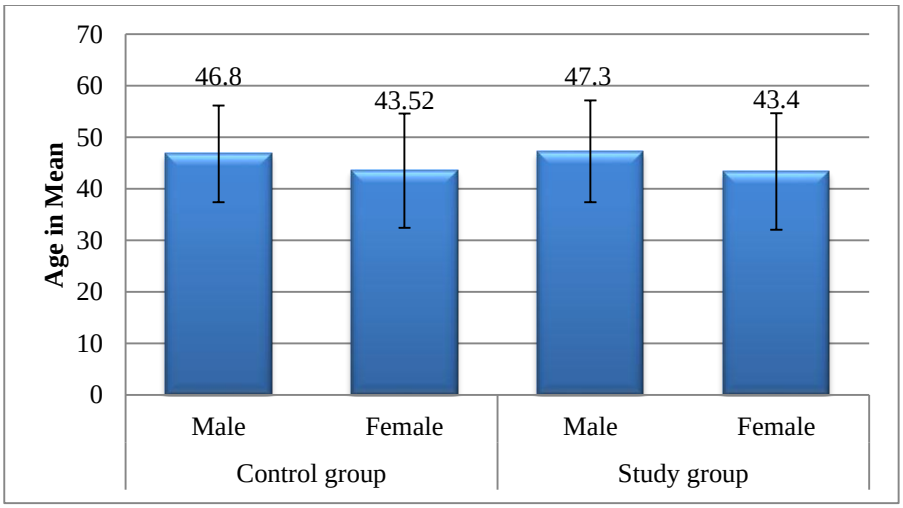
Age:

Table 5.1

Group	Age	Mean	S.D
Control	Male	46.8	9.4
Control	Female	43.52	11.1
Study	Male	47.3	9.9
Study	Female	43.4	11.3

Table 5.1 gives the mean age for males and females in the control group and study group. The mean age for males in the control group is 46.8 years with a standard deviation of 9.4 and the mean age in the study group is 47.3 years with a standard deviation of 9.9. The mean age for females in the control group is 43.52 years with a standard deviation of 11.1 and the mean age in the study group is 43.4years with a standard deviation of 11.3.

Figure 5.1



Gender:

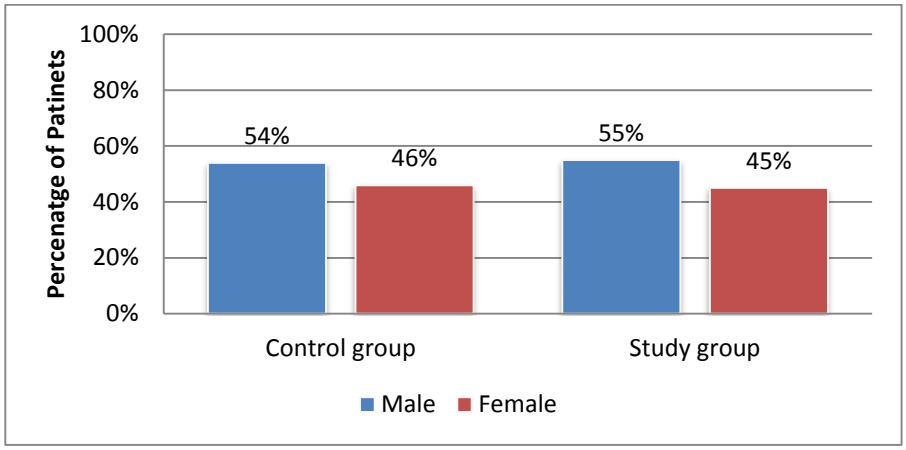
The sex wise distribution among controls and patients are as follows:

Table 5.2

Gender	Control group	Study group
Male	54%	55%
Female	46%	45%

Table 5.2 gives the sex wise distribution among the control group and study group. 54% of males and 46% of females were under control group and 55% of males and 45% of females were included in the study group.

Figure 5.2



Distribution of different parameters:

Table 5.3

Parameters	Group	Mean	Std. Deviation	P value
BMI	Control group	23.35	1.07	0.008
	Study group	24.06	2.46	
AGE	Control group	45.34	10.32	0.872
	Study group	45.58	10.73	
FPG	Control group	91.68	5.86	<0.0001
	Study group	96.53	8.73	
INSULIN	Control group	8.04	1.82	0.001
	Study group	10.85	7.99	
HDL	Control group	47.84	7.61	<0.0001
	Study group	40.72	7.03	
TG	Control group	111.63	21.52	<0.0001
	Study group	146.78	49.64	
HOMA-IR	Control group	1.82	0.43	<0.0001
	Study group	2.62	2.03	

Table 5.3 shows the mean and standard deviation of different parameters between the control group and study group. The mean BMI of the control group is 23.35 kg/m^2 and of the study group is 24.06 kg/m^2. The mean BMI of the study group is greater than that of the control group with a P value of 0.008. The mean age of the control group is 45.34 and of the study group is 45.58 having a P value of 0.872. Hence the age factor shows no significance.

The mean fasting plasma glucose of the control group is 91.68 mg/dl with a standard deviation of 5.86. The mean fasting plasma glucose of the study group is 96.53 mg/dl with a standard deviation of 8.73. Thus the mean fasting plasma glucose of the study group is higher than that of the control group with a P value of < 0.0001.

The mean serum insulin level of the control group is 8.04 μIU/ml with a standard deviation of 1.82. The mean serum insulin level of the study group is 10.85 μIU/ml with a standard deviation of 7.99. The mean serum insulin level of the study group is greater than the control group with a P value of 0.001.

The mean HDL level of the control group is 47.84 mg/dl with a standard deviation of 7.61. The mean HDL level of the study group is 40.72 mg/dl with a standard deviation of 7.03. Thus the mean HDL level of the study group is lower than that of the control group with a P value of <0.0001.

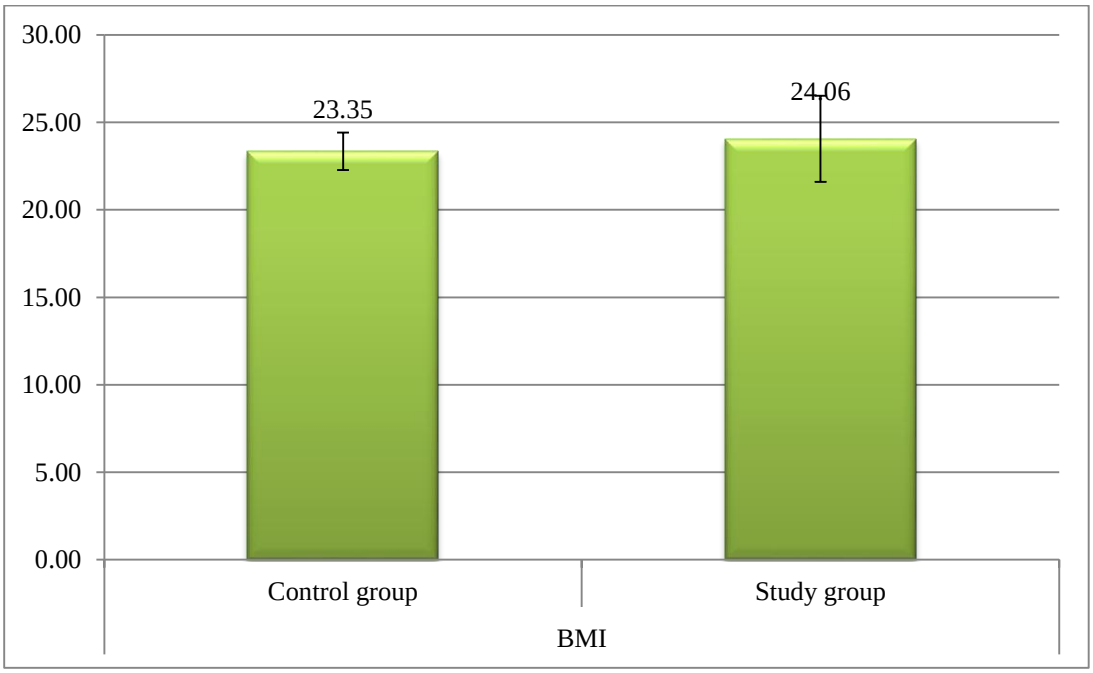
The mean triglyceride level of the control group is 111.63 mg/dl with a standard deviation of 21.52. The mean triglyceride level of the study group is 146.78 mg/dl with a standard deviation of 49.64. Thus the mean triglyceride level

of the study group is greater than that of the control group with a P value of <0.0001.

The mean HOMA-IR value of the control group is 1.82 with a standard deviation of 0.43. The mean HOMA-IR value of the study group is 2.62 with a standard deviation of 2.03. Thus the mean HOMA-IR value of the study group is greater than that of the control group with a P value of <0.0001.

Comparison of BMI between control group and study group:

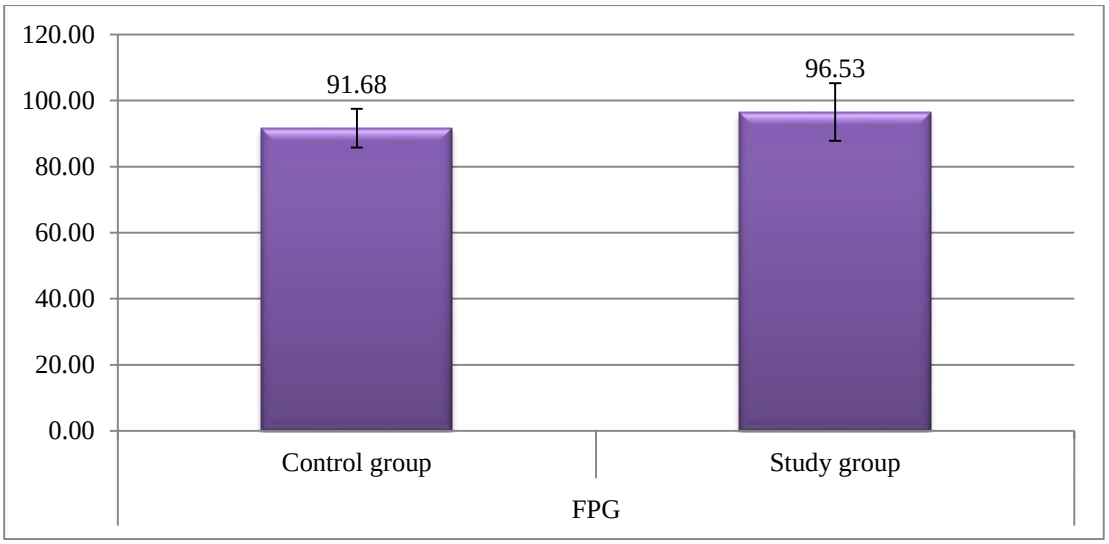
Figure 5.3



The average BMI for control group is 23.35 kg/m^2 and for study group is 24.06 kg/m^2.

Comparison of fasting plasma glucose between control group and study group:

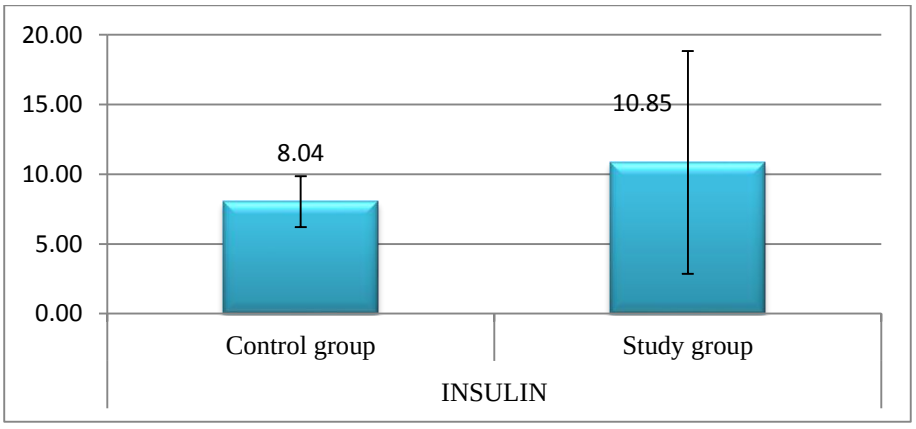
Figure 5.4



The average fasting plasma glucose of control group is 91.68 mg/dl and of study group is 96.53mg/dl.

Comparison of serum insulin level between control group and study group:

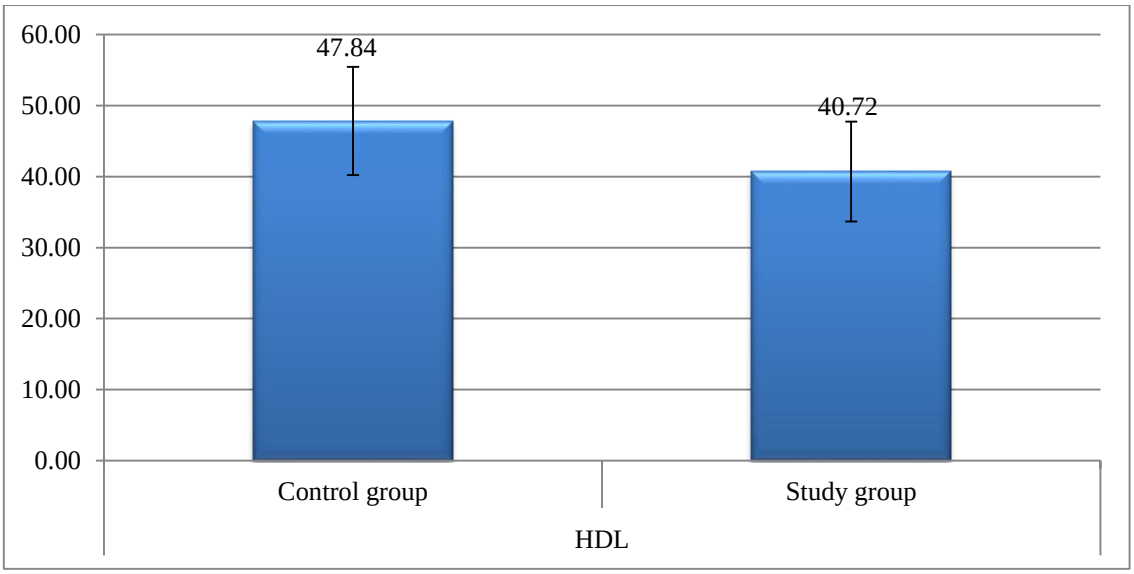
Figure 5.5



The average insulin level in control group is 8.04 µIU/ml and in study group is 10.85 µIU/ml.

Comparison of serum HDL between control group and study group:

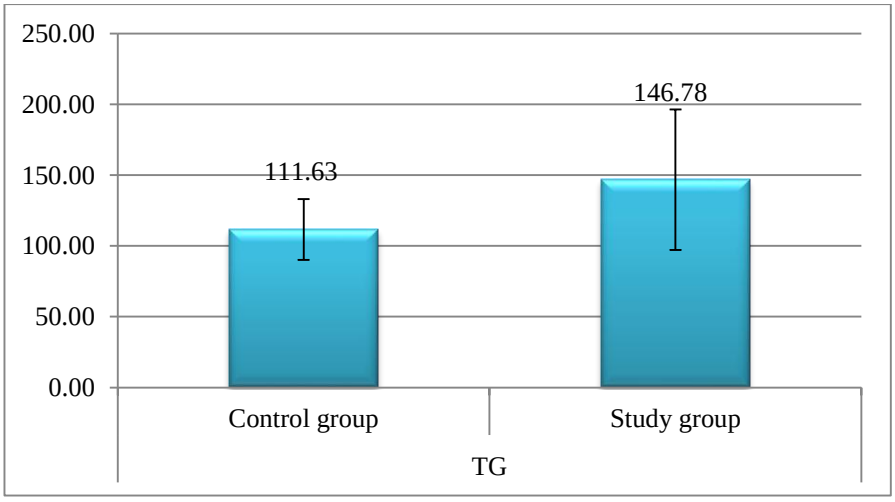
Figure 5.6



The average serum HDL of control group is 47.84 mg/dl and of study group is 40.72 mg/dl.

Comparison of triglycerides between control group and study group:

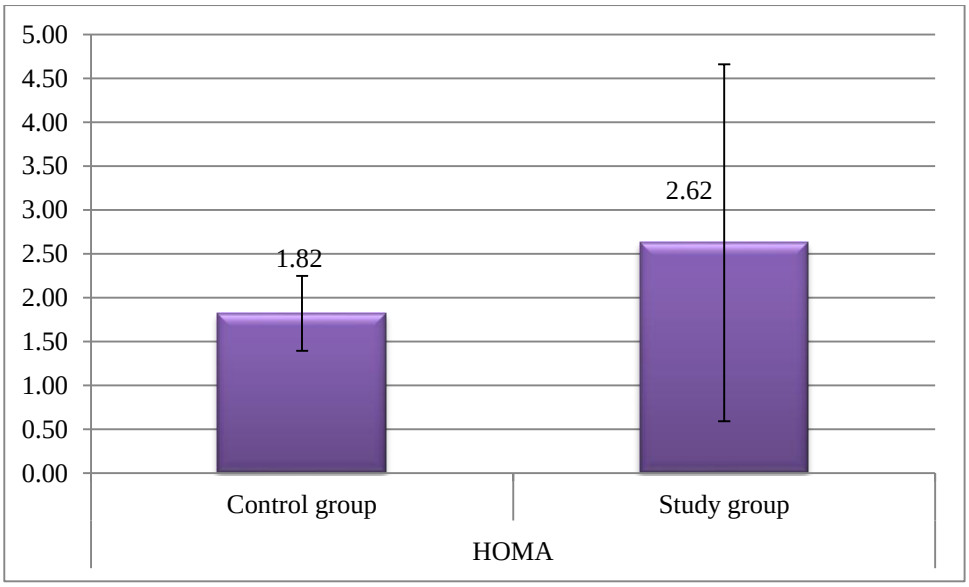
Figure 5.7



The average serum triglyceride level of control group is 111.63 mg/dl and of study group is 146.78 mg/dl.

Comparison of HOMA-IR values between control group and study group:

Figure 5.8



The average HOMA-IR of the control group is 1.82 and of study group is2.62.

Discussion:

Psoriasis is associated with significant morbidity and systemic manifestations. The association of variety of medical conditions in psoriasis may be based on sharing of common risk factors and pathophysiology.[99]The present study was carried out to find the association between psoriasis and insulin resistance. The associated biochemical parameters fasting serum insulin, fasting plasma glucose, serum high density lipoproteins and serum triglycerides were estimated. The level of insulin resistance was calculated using HOMA-IR.

The average fasting serum insulin in psoriasis patients was 10.85 μIU/ml and found significantly higher than that of the control group (8.04 μIU/ml). The high serum insulin levels indicate the feasibility of insulin resistance in psoriasis patients. Similar statistical significance was also noted by Uysal S and colleagues. The possible mechanism could be due to the release of adipokines and cytokines in psoriasis patients that impair the insulin sensitivity. The serum insulin levels become high in these patients. The higher concentration of serum insulin levels correlated positively with the disease activity.[100]

The average fasting plasma glucose of our study group was 96.53 mg/dl and of control group was 91.68 mg/dl. The study group shows a statistically significant higher level of fasting plasma glucose on comparing with controls. The high fasting glucose levels were also reported in non diabetic psoriasis patients by Baeta IG and colleagues. [101]There was no statistical difference in fasting plasma glucose between

psoriasis cases and controls in an epidemiological study at Bangalore by Gopal MG.[102]

The level of insulin resistance in our study showed a value of 2.62 in psoriasis patients which is found to be significantly higher than the value 1.82 of the control group. The high serum insulin and insulin resistance correlated with several studies including a cross sectional study at Burdwan. Krishnamoorthy and coworkers had reported a HOMA-IR value of 3.5 in psoriasis patients and 1.4 in controls which supports our study. Boehncke et al., had also noted signs of IR in psoriasis patients.

The possible mechanism behind this association between psoriasis and IR could be due to inflammatory cytokines. There is an overproduction of cytokines in psoriasis patients for example tumour necrosis factor alpha which play important roles in the pathways that regulate insulin sensitivity. Their varied actions on pathways include impairment of insulin signaling by inhibition of tyrosine kinase activity of insulin receptor, activation of peroxisome proliferator activated receptor (PPAR) which modulates glucose metabolism and by suppression of adiponectin secretion from adipocytes, all factors contribute to IR.[103]

In the present study, the average serum HDL in psoriasis patients was 40.72mg/dl and in control group was 47.84 mg/dl. The serum HDL levels were found significantly low in psoriasis patients than controls. The average serum triglyceride value in psoriasis patients was 146.78 mg/dl and in control group was 111.63 mg/dl. The serum triglyceride values in psoriasis patients were significantly

higher than that of controls. This statistically significant difference in HDL and triglyceride levels was also noted in a case control study by Taheri Sarvtin M and colleagues. The abnormality in plasma lipid mechanism occurs in psoriasis and it is probably related to alterations in insulin sensitivity and secretion.[104]

In conditions of IR, there is increased oxidation of free fatty acids in serum which provides substrate for triglyceride synthesis in liver and hence the hepatic release of triglyceride rich VLDL into the serum is increased. The lipid profile is thus altered leading to increased triglycerides and decrease in HDL-cholesterol fraction.[105]

There are much more evidences that psoriasis is associated with unfavorable lipid profile and enhanced atherosclerosis. The atherogenic trend in the lipid levels of psoriatic patients demonstrated by significantly high triglyceride and low HDL levels were also reported by Akkara Veetil BM and colleagues. So it is likely that psoriasis predispose the individuals to dyslipidemia.[106]

The average BMI calculated for psoriasis patients was 24.06 kg/m^2 and that of the control group was 23.35 kg/m^2showing a statistically significant difference between patients and controls. These values correlated with the findings of Armstrong AW and colleagues which showed a slightly increased risk of developing obesity in psoriasis patients when compared to controls. The precise mechanism of association between psoriasis and obesity was unknown. Research studies suggested that activation of inflammatory macrophages cause stimulation of adipose tissue to secrete adipokines. The coexistence of psoriasis and obesity could

be attributed to the action of adipokines. In addition to genetic and immune mediated mechanisms, behavioral factors such as reluctance to engage in physical activities might play an important role in connecting psoriasis and obesity.[107]

There are many studies in various regions including India evaluating psoriasis patients during the path of the disease process. Our study had included patients who were not on systemic treatment. Systemic medications for psoriasis are considered as independent risk factors for metabolic abnormalities in psoriasis patients.

Conclusion:

The present study was done to estimate the level of insulin resistance and to study the associated biochemical parameters such as fasting plasma glucose, serum high density lipoproteins and triglycerides in psoriasis patients who attended the Outpatient Department of Dermatology, Sree Mookambika Institute of Medical Sciences, Kulasekharam.

Psoriasis is a chronic autoimmune inflammatory skin disease with a genetic background. The inflammatory mediators that are increased in psoriasis are supposed to interfere with the various functions of insulin and predispose to IR. As expected the IR was found significantly high in psoriasis patients.

The main finding in the present study was significantly high level of serum insulin in psoriasis patients. The other findings of the study were increased insulin resistance, low HDL and high triglyceride levels in these patients. IR provokes lipolysis and release of free fatty acids into the circulation which provide substrate for triglyceride synthesis and the hepatic release of triglyceride rich VLDL into the serum is increased. The lipid profile is thus altered leading to increased triglycerides and decrease in HDL-cholesterol fraction.

The insulin resistance and lipid derangements predispose the individuals to the risk of atherosclerosis and cardiovascular disorders. There is impairment of reverse cholesterol transport and augmentation in the process of atherosclerosis. IR also causes a reduction in energy supply to the myocardium and a change in

substrate utilization from glucose towards fatty acids. The hypercoagulable, prothrombotic and oxidative state predispose to cardiovascular disease.

Thus we see that psoriasis is no longer a skin disease, rather it has implications over vital organ systems of the human body. It should always be kept in mind that skin disorders may give a clue to the existence of internal abnormalities. Numerous studies have also evidenced that cutaneous changes may be a manifestation of internal illness. There should be an expanding attention in psoriasis patients beyond skin pathology to rule out systemic abnormalities. Knowledge in depth about the biochemical basis of the association will help to develop substantial modifications in the early diagnosis and management of the internal consequences of psoriasis. The screening for insulin resistance in psoriasis patients provide a great opportunity to alert and motivate for proper dietary and weight maintenance together with life style changes.

Summary

Psoraisis is an autoimmune skin disease influenced by genetic and environmental factors. Psoriasis is predisposed to various comorbidities such as diabetes, hypertension, atherosclerosis and cardiovascular disease due to the underlying autoimmune etiology. The autoimmune etiopathogenesis associated with increase in interleukins and TNF α form a connective link between psoriasis and IR.

IR is defined as a lack in the normal physiological effects of insulin on target tissues. IR will lead to impaired glucose tolerance state and finally T2DM. The metabolic consequences of increased insulin level or hyperinsulinemia have profound effects on lipid metabolism leading to decreased HDL and high triglyceride levels. This altered lipid parameters will predispose the patients to atherosclerosis and cardiovascular illness.

The present study was conducted to find out serum insulin levels in psoriasis patients. Insulin resistance was calculated and found to be significantly higher in patients. Fasting blood sugar, serum HDL and triglycerides were the other parameters estimated and significant difference was noted in these parameters between patients and controls. There was a statistical difference in BMI between patients and controls. IR calculated in our study had crossed the upper limit of normal.

Hence the results of the present study suggested that reducing IR by a multidisciplinary approach can protect the patient from metabolic alterations that predispose to T2DM and cardiac illness.

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(DLQI), Psoriatic Arthritis Quality of Life (PsAQOL), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), Psoriatic Arthritis Response Criteria (PsARC), Psoriatic Arthritis Joint Activity Index (PsAJAI), Disease Activity in Psoriatic Arthritis (DAPSA), and Composite Psoriatic Disease Activity Index (CPDAI). Arthritis Care Res (Hoboken). 2011;63 Suppl 11:S64-85.

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